

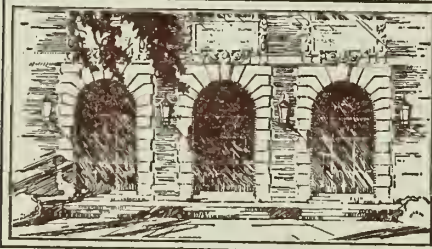
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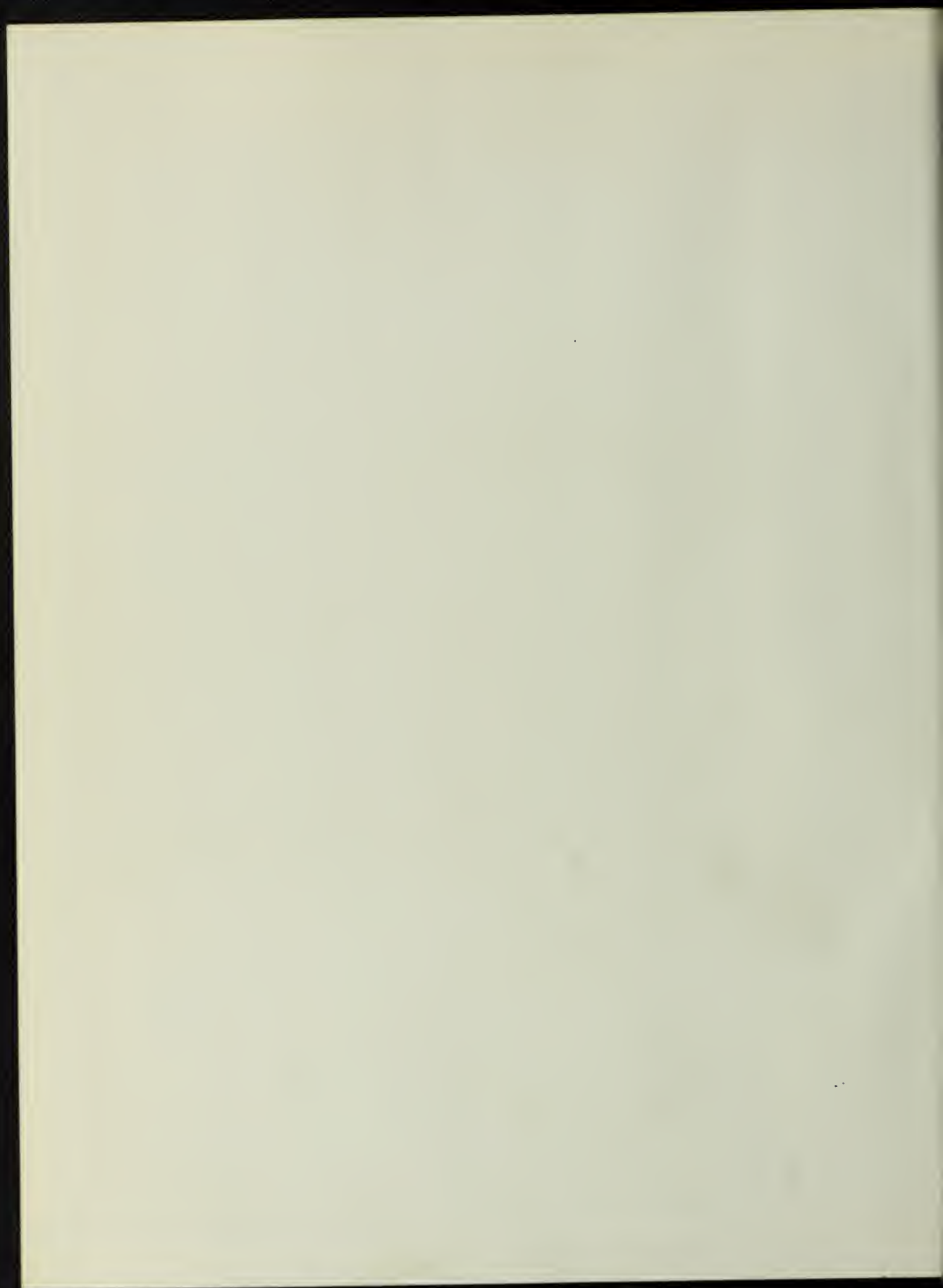
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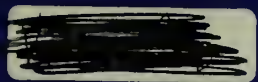
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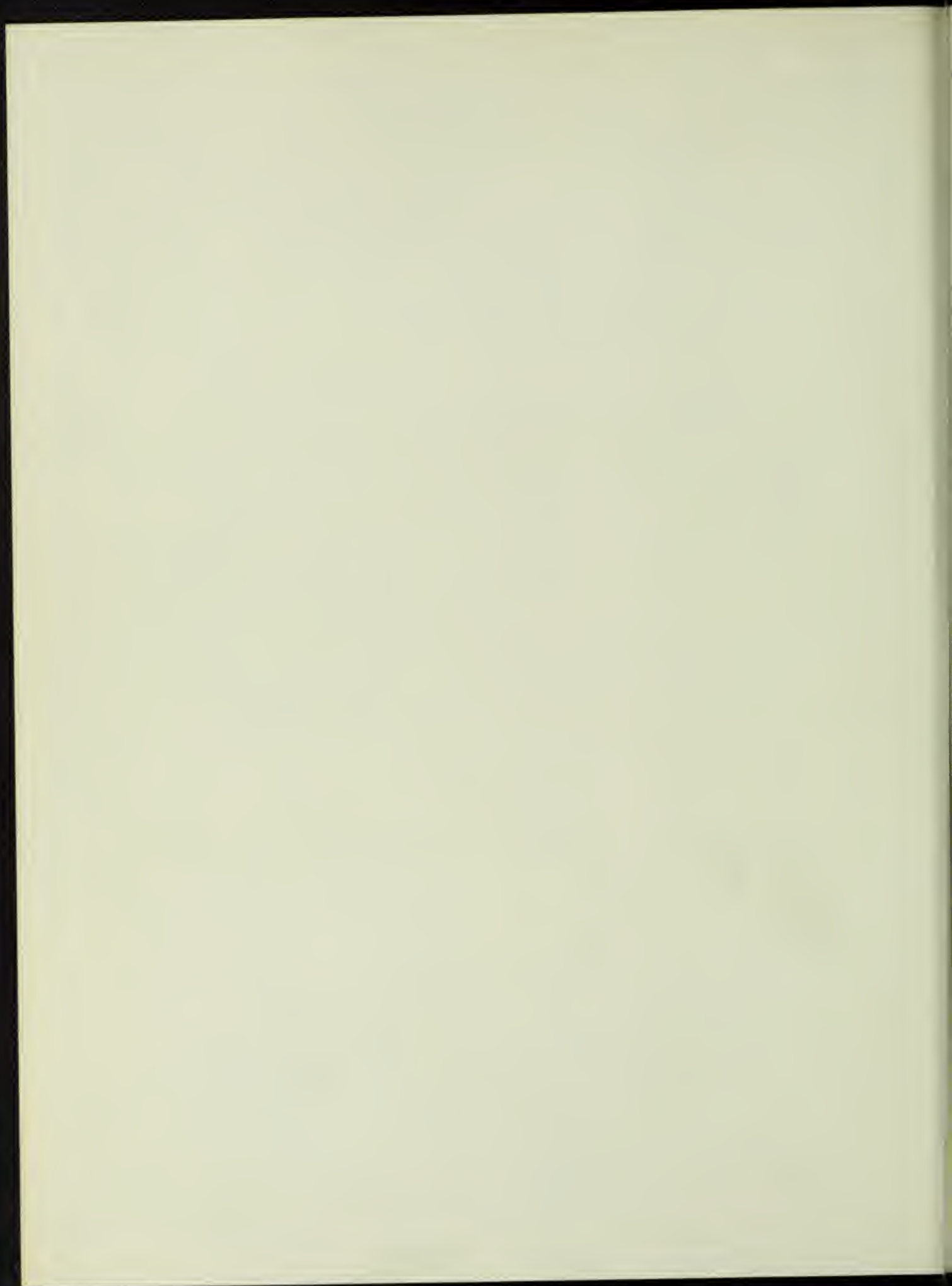
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**Vol. 13
No. 9**

**CARCINOGENESIS
ABSTRACTS**

National Cancer Institute

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Public Health Service National Institutes of Health



CARCINOGENESIS ABSTRACTS

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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

Carcinogenesis Abstracts is normally published monthly. Volume XIII covers the scientific literature published from Jan 1975 through Dec 1975. To increase the usefulness of *Carcinogenesis Abstracts*, Volume XIII, a Wiswesser Line Notation index and a Chemical Abstracts Service Registry Number index have been provided. These indexes reference compounds described in abstracted articles. A cumulative subject, author, CAS Registry Number, and Wiswesser Line Notation index for Volume XIII will be published shortly after the final regular issue.

Carcinogenesis Abstracts is available free of charge to libraries and to individuals who have a professional interest in carcinogenesis. Requests for *Carcinogenesis Abstracts* from qualified individuals should include statements of their relationship to carcinogenesis research. All correspondence should be addressed as follows.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations found in *Chemical Abstracts Service Source Index*, 1907-1974 Cumulative, are used. New journals are verified in *New Serial Titles* and abbreviated according to *International Standard ISO 833*. An asterisk indicates the author to address (other than the primary) in requesting reprints.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	Ind.	Indonesian
Ara.	Arabic	Ita.	Italian
Bul.	Bulgarian	Jpn.	Japanese
Chi.	Chinese	Kor.	Korean
Cro.	Croatian	Lav.	Latvian
Cze.	Czech	Lit.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
Eng.	English	Por.	Portuguese
Est.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fle.	Flemish	Ser.	Serbo-Croatian
Fre.	French	Slo.	Slovak
Geo.	Georgian	Spa.	Spanish
Ger.	German	Swe.	Swedish
Gre.	Greek	Tha.	Thai
Heb.	Hebrew	Tur.	Turkish
Hun.	Hungarian	Ukr.	Ukrainian
Ice.	Icelandic	Vie.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

A	angstrom(s)	M	molar
ACTH	adrenocorticotrophic hormone	mM	millimolar
ADP	adenosine diphosphate	μ M	micromolar
AMP	adenosine monophosphate	mOsm	milliosmolar
ATP	adenosine triphosphate	mEq	milliequivalents
BCG	Bacillus Calmette Guerin	min	minute(s)
bid	twice daily	mo	month(s)
C	degrees centigrade	MTD	maximum tolerated dose
cal	calorie(s)	N	normal concentration
kcal	kilocalorie(s)	NAD	nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADH	reduced nicotinamide adenine dinucleotide
Ci	curie(s)	NADP	nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NADPH	reduced nicotinamide adenine dinucleotide-phosphate
μ Ci	microcurie(s)		
cm	centimeter(s)	ng	nanogram(s) (10^{-9})
CNS	central nervous system	od	once daily
cpm	counts per minute	Pa	ambient pressure
dL	deciliter(s)	PAS	periodic acid-Schiff
ml	milliliter(s)	pg	picogram(s) (10^{-12})
μ l	microliter(s)	pgEq	picogram equivalent
DNA	deoxyribonucleic acid	po	orally
ED ₅₀	median effective dose	ppb	parts per billion
EDTA	ethylenediamine tetraacetic acid	ppm	parts per million
ESR	erythrocyte sedimentation rate	qid	four times daily
g	gram(s)	qod	every other day
kg	kilogram(s)	QO ₂	oxygen quotient
mg	milligram(s)	R	roentgen(s)
μ g	microgram(s)	RBC	red blood cells (erythrocytes)
Hb	hemoglobin	RNA	ribonucleic acid
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
ic	intracerebral	SGOT	serum glutamic-oxalacetic transaminase
icav	intracavitary	SGPT	serum glutamic-pyruvic transaminase
id	intra-dermal	SRBS	sheep red blood cells
ILS	increased life span	TCD	tissue culture dose
im	intramuscular	TCD ₅₀	median tissue culture dose
ip	intraperitoneal	tid	three times daily
ipl	intrapleural	U	unit(s)
it	intratumorous	mU	milliunit(s)
IU	International Unit	UV	ultraviolet
iv	intravenous	vol	volume
K _m	Michaelis constant	WBC	white blood cells (leukocytes)
LD	lethal dose	wk	week(s)
LD ₅₀	median lethal dose	wt	weight
m	meter(s)	x	times
mm	millimeter(s)	yr	year(s)

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4801 CARCINOGENESIS. (Eng.) Calvin, M. (Lab. Chemical Biodynamics, Univ. California, Berkeley, Calif. 94720). *Naturwissenschaften* 62(9): 405-413; 1975.

The nature of primary transformation and how it may result from the action of viruses, chemicals, radiation, and/or interactions among them are discussed. Special emphasis is placed on the effects of chemical carcinogens on enzymes, cells, tissue cultures, and animals. The reactive and enzymatically activated chemical carcinogens are discussed; the mode of action is probably electrophilic. The alkylation of some nucleotide bases is described, and studies of acetylaminofluorene derivatives suggest that RNA or DNA intercalation is an essential step of chemical carcinogenesis. Studies of the carcinogenicity and the chemistry of the polycyclic aromatic hydrocarbons, and especially of benzo[a]pyrene, have shown the induction of aryl hydrocarbon hydroxylase. The idea that the epoxide is an obligatory intermediate in the carcinogenic activity of benzo[a]pyrene is then presented. Postulated reactions of the covalent linkage of benzo[a]pyrene to nucleic acid components are illustrated, and experiments showing a photochemical coupling of benzo[a]pyrene to N-methylcytosine have demonstrated a real product formed between a model of a nucleic acid component and a carcinogen. Biological considerations suggest that chemical carcinogenesis induces the insertion or rearrangement of large pieces of information *via* its reactivity with one or more of the nucleic acid bases of DNA or RNA. Studies have demonstrated an RNA-dependent DNA polymerase type of activity in the RNA oncogenic viruses, and have documented the effectiveness of rifamycin derivatives in inhibiting that activity. Several synthetic modifications of rifamycin are discussed. It is noted that the drug can apparently distinguish those enzymes required for virus replication only from those which are also required for transformation. It is further suggested that the induction of enzyme activity might increase the probability of inserting viral information; studies employing 4-nitroquinoline oxide and an adenoma virus are cited, and a synergistic effect is demonstrated. Thus it appears that chemicals may trigger the expression of the kind of information represented by that contained in an oncogenic virus and already present in the cell. (41 references)

4802 THE VALIDITY OF LONG-TERM BIOASSAYS IN CARCINOGENICITY TESTING. (Eng.) Tomatis, L. (International Agency Res. Cancer, Lyon, France). *Proc. Int. Cancer Congr.* 11th. Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 87-93.

The validity and limitations of long-term bioassays are discussed. Some of the guidelines for the conducting of animal experiments are presented; these note a definite tendency to consider an observation of at least two years as an adequate duration of a negative test. While neonatal treatment of animals is considered to be a very sensitive and

sometimes sufficient testing model, it is not recommended as a general procedure. Likewise, although prenatal exposure may reveal a carcinogenic effect at unusual target sites and at very low levels of exposure, it too cannot be recommended as a general routine procedure replacing conventional testing on young adult animals. Despite a general dissatisfaction regarding the time and expense of long-term testing, such testing is shown to be useful in preventing cancer; the most often quoted example is that of the experimentally-shown carcinogenicity and subsequent prohibited use of acetylaminofluorene. In addition, present regulations recommend a zero food tolerance of chemicals for which experimental evidence of carcinogenicity exists. Factors regarding both the objective and social validity of experimental results are discussed. Different types of relationships may exist between experimental evidence obtained in long-term bioassays, the possible human hazard and the adoption of preventive measures; illustrative examples are presented. Whereas initial human and experimental evidence of the carcinogenicity of β -naphthylamine was deemed insufficient, further epidemiological studies eventually promoted preventive measures against the hazard. In the cases of stilbestrol, bis(chloromethyl) ether, and vinyl chlorides, experimental evidence of their carcinogenic effects preceded such observations in man; however, restrictions on their use occurred only after retrospective (human) epidemiological surveys. In contrast, the use of DDT was banned or severely restricted due to environmental considerations, prior to any epidemiological studies. Within the literature, there is an evident preoccupation with warning about unduly extrapolating from experimental data to man. However, monographs prepared on 164 individual suspect chemical carcinogens show 17 to be carcinogenic in man, and an additional 82 are carcinogenic in one or more animal species. It is proposed that a general consensus on the validity of experimental results should be reached and should replace the procedure of preventing *a posteriori* the occurrence of cancer in man. (37 references)

4803 THE CHEMISTRY OF SMOKED FOODS: A REVIEW. (Eng.) Gilbert, J. (Ministry of Agriculture, Fisheries and Food, Food Science Div., Colney Lane, Norwich NR4 7UA, England); Knowles, M. E. *J. Food Tech.* 10(3):245-261; 1975.

Recent advances in the chemistry of the 'smoke' fraction of smoked foods are reviewed; the factors considered include the constituents found in woodsmoke and their formation and significance in terms of flavor, color, preservative, and food safety. Important reactions occurring during pyrolysis of cellulose, hemicellulose, and lignin are discussed. Components of various types of woodsmoke are analytically identified, as is the composition of commercial 'liquid smoke' condensates. The results of analyses of some smoked meat products are reported, as are the results of studies on smoked condensates and selective absorption of smoke constituents. Phenols have been found to be major contributors to the flavor of smoked foods, and the ultimate flavor apparently results from a complex blend of the smoke

and original food flavors and/or reaction of smoke constituents with the surface proteins. Typical color formation is due to browning involving carbonyl-amino reactions. 3,4-Benzpyrene is the most commonly specifically determined polycyclic hydrocarbon in foodstuffs, and its concentrations in a number of foods are presented. A hypothetical scheme for the mechanism of formation of such polyaromatics during pyrolysis is presented. Further considerations include the influence of smoke generation conditions, penetration into foodstuffs, deposition of polycyclic hydrocarbons casings, and the levels of such polyaromatics in liquid smoke preparations. Future developments in woodsmoke chemistry should be directed at identifying and assessing the significant flavor and color components, thereby allowing the development of much improved liquid smokes and smoke flavors for increased usage by the food industry. (71 references)

- 4804 ORAL CONTRACEPTIVES AND LIVER TUMOURS.
(Eng.) Anonymous. *Lancet* 1(7922):1414-1415; 1975.

The cancer risk associated with diethylstilbestrol, testosterone, estrogens, and progestagens is briefly discussed. Animal studies have shown that sex hormones with estrogenic or progestagenic ability have carcinogenic potential; tumors are most commonly found in the liver, pituitary, breast, and female reproductive system. However, these tumors usually occur at the higher doses tested. There is little evidence that estrogens and progestagens, taken separately or together, cause benign or malignant hepatomas in animals. Few epidemiologic studies on the human female have been undertaken; however there may be a correlation of histologically benign, but often fatal, liver tumors with oral contraceptives. (2 references)

- 4805 A CRITICAL REASSESSMENT OF THE EVIDENCE BEARING ON SMOKING AS THE CAUSE OF LUNG CANCER. (Eng.) Sterling, T. D. (Computer Science Program, Simon Fraser Univ., Vancouver, British Columbia, Canada). *Am. J. Public Health* 65(9):939-953; 1975.

The results and methods of epidemiological studies implicating smoking as a major cause of lung cancer were reviewed. Conclusions concerning the hazards of cigarette smoking are primarily based on seven prospective surveys, all of which employed successions of "selection factors" in assembling their study populations. A representative American Cancer Society (ACS) study population contained 10% fewer males, 10% more females, 90% fewer blacks, and more highly educated, Protestant, and native American persons than the general U.S. population. In addition to such nonrepresentative samples, various subtle psychological and sociological effects on selecting the final group of subjects are suspected. These may include the tendency of the ACS volunteers to select smokers who were ill over healthy smokers for inclusion in the study. In comparing the distribution of causes of death, the ACS study found significantly more deaths from lung cancer, breast

cancer, emphysema, and coronary heart disease than would be expected from a segment of the U.S. population. Contrasting results were obtained in a Japanese study which avoided self-selection bias by obtaining information on all individuals over 40 yr living in particular districts. Largely equal mortality was found among Japanese smokers and non-smokers. The high incidence of cancer of the pancreas, bladder, lung, and esophagus suggests that the members of the Japanese population had a high occupational exposure to irritant air pollutants and industrial carcinogens; the occupational background of smokers and nonsmokers is of paramount importance in determining the incidence of lung cancer. Macrostatistical population studies reveal a leveling off of lung cancer mortality, despite increasing cigarette consumption. Other macrostatistical findings in conflict with the assumed relation of smoking and lung cancer are: (1) large differences in the geographical distribution of smoking and lung cancer patterns, (2) migrant population lung cancer mortality rates falling between the rates of original country and the new host country, (3) pronounced occupational differences in lung cancer incidence, and (4) rapidly decreased lung cancer incidences after cessation of smoking. The author stresses the fact that the causes of cancer are complex, and that statistical studies on the effects of smoking must be carefully analyzed. (116 references)

- 4806 TOBACCO RADIOACTIVITY AND CANCER IN SMOKERS.
(Eng.) Martell, E. A. (Nat. Center for Atmospheric Res., P.O. Box 3000, Boulder, Colo. 80303). *Am. Sci.* 63(4):404-412; 1975.

The possible cancer risks and other consequences on health of insoluble radioactive smoke particles and of insoluble alpha-emitting particles from other sources are discussed after a brief review of the processes which lead to the formation of insoluble radioactive smoke particles. It was recently found that ^{210}Pb is highly concentrated in a small number of insoluble smoke particles. The ^{210}Pb and ^{210}Po in the insoluble smoke particles which persist in lung tissue are highly localized and involve particles and/or clusters with activities ranging from less than 10^{-6} pCi to more than 10^{-4} pCi at each focal point. For alpha radiation-induced cancer, the risk relationship can be written in the general form, tumor risk = $k_i n_c \lambda_c^2 R^2 t^3$, where n_c is the number of cells at risk; λ_c is the mitotic rate of the singly mutated cells; k_i is a proportionality constant; R is the alpha dose rate; and t is the exposure period. Although this formula is highly oversimplified, it does express the general relationship between tumor risk and period of exposure for various organs and indicates the exceptional tumorigenicity to be expected for spaced alpha interactions in tissue of relatively high mitotic activity. Studies of inhaled insoluble plutonium oxide particles in mammals have demonstrated that some particles deposited in pulmonary spaces are slowly translocated to the respiratory lymph nodes, liver, and bone. These particles have residence times for the persistent particles of about two years in the lung, decades in lymph nodes and liver, and longer in skeletal tissue. This leads to the conclusion that internal alpha-emitters, rather than cosmic rays or

other natural sources of radiation, may be the principal agent of radiation-induced cancer in man. Published evidence indicates that atherosclerosis plaques may be arterial tumors and that an excess of alpha activity is present at the calcified plaque site, suggesting that radiation is the possible agent of mutagenesis. The substantially enhanced risk of early coronaries among cigarette smokers also suggests that insoluble radioactive smoke particles may find their way into arterial tissue and contribute to the earlier development of atherosclerosis plaques in this group. It is also suggested that cancers previously thought to be caused by chemical carcinogens in cigarette smoke, combustion products and other common urban pollutant mixtures may, in fact, be caused by insoluble alpha-emitters. (38 references)

- 4807 THE ROLE OF THE IMMUNE RESPONSE IN ONCO-GENESIS. (Eng.) Jeejeebhoy, H. F. (Fox Chase Cancer Center., Philadelphia, Pa. 19111). *In Vitro* 11(3):166-172; 1975.

Ways in which an immune response to tumor-specific transplantation antigens (TSTA) may modify the intrinsic proliferative and infiltrative capacities of tumor cells were investigated. Mice were injected with cells from three different syngeneic methylcholanthrene-induced tumor lines. The cellular and humoral antitumor immune responses of their peripheral blood lymphocytes and sera were studied by *in vitro* techniques. Both normal lymphocytes and normal fibroblasts had the capacity to nonspecifically stimulate colony formation by tumor cells. Five days after inoculation of tumor cells, lymphoid cells from mice inoculated with tumor cells stimulated *in vitro* colony formation by tumor cells to a greater degree than did cells from uninoculated animals. The stimulatory effect of lymphocytes obtained from mice five days after inoculation of tumor cells on *in vitro* tumor growth was potentiated by the presence of low concentrations (0.2%) of serum from these same animals. Twelve days after inoculation, there was a tendency for immune cells to specifically inhibit rather than stimulate, tumor growth. Consideration of the three stages of tumor progression suggests that the early and presumably weak immune response to TSTA is stimulatory for tumor growth, whereas it is inhibitory in its later, fully developed form. (30 references)

- 4808 GRANULOPOIESIS IN CULTURES OF HUMAN HAEMOPOIETIC CELLS. (Eng.) McCulloch, E. A. (No affiliation given). *Clin. Haematol.* 4(3):509-533; 1975.

Views of the origin of granulopoiesis from pluripotent stem cells are presented, and studies of human granulopoietic progenitors in culture are summarized. Three independently regulated myeloid pathways of hemopoietic differentiation, originating from a common pool of pluripotent stem cells, are suggested in both animal and human studies. The independent regulation is explained in terms of the functional anatomy of the hemopoietic system, while both long and short range mechanisms are implicated. Colony

and suspension cell culture methods are described; general experimental problems and specific methodological problems of hemopoietic cell cultures are discussed. Studies of cellular interactions in normal granulopoiesis in culture find numerous stimulators of granulopoietic progenitors in murine hemopoietic tissues, but an apparent independence of human granulopoietic progenitors from colony stimulating activity (CSA)-producing cells. It is suggested that granulopoiesis in such cultures depends upon interactions between granulopoietic progenitors and CSA-producing cells, both of which are found present in human marrow. Studies of granulopoietic progenitors capable of forming colonies in culture are reviewed in depth, and four molecular species with colony-stimulating activity are potentially identified. The subcellular source of high molecular weight (non-dialyzable) CSA is also being studied. The capacity of adult hemopoietic tissues to stimulate granulopoiesis is found localized in the monocytes, and a model for the regulation of granulopoiesis in culture is presented. Applications of methods developed for the study of normal granulopoiesis in culture to studies of leukemia are described, and various problems of interpreting results are discussed. Growth patterns are suggested as useful in determining the prognosis and assessment of remission status. Studies of granulopoietic colony stimulating activity and CSA-producing cells in leukemia are noted; in addition, abnormalities and variables found in cultures from preleukemic, cyclic neutropenic, and chronic neutropenic patients are discussed. Correlations between clinical findings and culture data are attempted. (90 references)

- 4809 MORPHOLOGICAL CLASSIFICATION OF MALIGNANT LYMPHOMAS: ULTRASTRUCTURAL, CYTOCHEMICAL AND IMMUNOLOGICAL RESULTS. (Eng.) Schaefer, H. E. (Pathologisches Institut der Universität zu Köln, Abteilung für Feinstrukturelle Pathologie, 5 Köln 41 Deutschland, Josef-Stelzmannstr. 9, West Germany); Kruger, G. R. F.; Fischer, R. *pathol. [Suppl.] (Berl.)* 6:21-29; 1975.

Several immunological and morphological features of malignant lymphomas are elaborated upon, and the evolving problems of the classification of unusual lymphomas are discussed. Membrane-bound surface immunoglobulins are convenient markers for B-cells and certain immunological cell types, e.g. IgM, appear to predominate in some of the histological types of lymphomas. However, studies of 184 patients have failed to correlate the different classes of malignant lymphomas with a constant surface immunoglobulin pattern. This is supported by the observations of polyclonal populations, T-cell and null-cell lymphomas, and the suggestion of neoplastic dedifferentiation of former B-cells. The detection of various intracellular lambda-chain crystalline inclusions in the blood lymphocytes of chronic lymphocytic leukemia further suggests a morphological hallmark of anaplastic deterioration of immunoglobulin synthesis. Many cytoplasmic PAS-positive inclusions represent merely glycogen or glycogen-like carbohydrates, as demonstrated in a case of giant follicular infiltration. The ambiguous significance of virus-like microtubular complexes in lym-

phocytes is also discussed. In addition to underlining the inadequacy of solitary parameters for purposes of classification, the recognition of hairy cell leukemia demonstrates the value of a seemingly inconspicuous cytological marker. Nomenclatures based on empiricism rather than on theories which can be short-lived should be employed. (40 references)

- 4810 ULTRASTRUCTURAL CHARACTERISTICS OF HUMAN TUMOR CELLS *IN VITRO*. (Eng.) Seman, G. (Texas Medical Center, Houston, Tex.); Dmochowski, L. In: *Human Tumor Cells in Vitro* edited by J. Fogh. New York, Plenum Press, 1975, pp. 395-485.

Procedures used to prepare tissue culture cells for electron microscopy are summarized. Descriptions are presented of the most significant ultrastructural features of human tumor cells in culture. Cells derived from epithelial tumors, sarcomas, and neoplasms of hematopoietic tissues are considered. The cells of epithelial tumor origin include HeLa, KB, and HEP-2 cells derived from carcinoma of the cervix, oral carcinoma, and laryngeal carcinoma, respectively, and also cells derived from melanomas, breast cancer, and lung cancer. The effects of cultivation conditions, of chemical and physical agents, and of viruses and mycoplasmas on the fine structure of some tumor cells are discussed. The chemical agents considered 5-bromodeoxyuridine, acridine orange, chloroquine, glycerol, poisons to the mitotic spindle, inhibitors of mitochondrial synthesis, and drugs that interfere with DNA and RNA synthesis. The physical agents examined are x-, UV-, and ruby laser-irradiation and supraoptimal temperatures. Viruses are considered mainly in relation to HeLa, KB, and HEP-2 cells, and include adenoviruses, vaccinia, herpes, influenza and parainfluenza, measles, poliovirus, and Newcastle disease virus. Although human tumor cells in prolonged cultures do not reveal any specific morphological markers of malignancy, the cells retain certain structural characteristics that provide important clues to their origin. The most rewarding approach in studying the fine structure of human tumor cells *in vitro* is a simultaneous analysis of structure and function. (297 references)

- 4811 CHROMOSOME ABNORMALITIES IN HUMAN TUMOR CELLS IN CULTURE. (Eng.) Biedler, J. L. (Memorial Sloan-Kettering Cancer Center, New York). In: *Human Tumor Cells in Vitro* edited by Fogh, J. New York, Plenum Press, 1975, pp. 359-394.

The use and objectives of karyotype analysis in determining the origin of putative human tumor cells in culture are evaluated. Following a brief description of the scope of culture techniques, early studies of human tumor lines are reviewed. In a discussion of initial attempts to establish permanent lines of normal (diploid) cells, the problems of instability of the diploid karyotype and the extensive heteroploidy of continuous cell lines of normal tissue origin are given particular attention. More recent endeavors have enabled the characterization of chromosomes of the cultured cells, and have revealed the *in vitro*

stability of the tumor cell karyotype. Studies of neuroblastoma cells in continuous culture have demonstrated chromosome numbers in the diploid range and distinctive and different marker chromosomes. The continuous culture of the neuroblastoma lines may enable the correlation of karyotype with morphological and growth characteristics, and the identification of the tissue of origin. A comparison of the distribution of modal chromosome numbers observed for tumor lines in continuous culture with those found in solid tumors suggests two major categories of tumor lines: near-diploid and hypo-hypertriploid. New techniques that can be utilized for chromosome identification include quinacrine fluorescence and Giemsa banding. It is concluded that: (a) knowledge of chromosome constitution of tumor lines is useful in a variety of ways, (b) the *in vitro* karyotype usually represents the karyotype of the original tumor tissue, and (c) karyotype abnormality of human cells in culture may be a reliable indicator of their malignant origin. (131 references)

- 4812 GENETIC PREDISPOSITION TO CANCER. (Eng.) Knudson, A. G., Jr. (Univ. Texas Health Science Center, Houston, Tex.). *Proc. Int. Cancer Congr. 11th. Vol. 4 (Cancer Campaigns, Detection, Rehabilitation, Clinical Classification)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 183-187.

The first three of the four genotypic categories which contribute to a predisposition to cancer are discussed: chromosomal, mendelian recessive, mendelian dominant, and polygenic. Chromosomal abnormalities usually do not cause predisposition to cancer. The two exceptions are trisomy or deletion. Down syndrome is a trisomic state which imparts susceptibility to cancer while the D deletion syndrome is associated with multiple anomalies and retinoblastoma. Although there is nearly a one-to-one correspondence between the Philadelphia chromosome and chronic granulocytic leukemia, the chromosomal abnormality is not necessarily antecedent. Somatically acquired chromosomal abnormalities are a feature of mendelian recessive disorders, e.g., Fanconi and Bloom syndrome, ataxia telangiectasia, and xeroderma pigmentosum. Chromosomal breakage is prominent in the first three; all four share a sensibility to sunlight and a susceptibility to one or more kinds of cancer. Other recessive disorders which predispose to cancer include the immune deficiency diseases, suggesting that the increased incidence of leukemia and lymphoma reflects a predisposing cell defect in the lymphopoietic system rather than an immunologic susceptibility to cancer. The upmost potent cancer genes are the mendelian dominants which cause specific site cancers (e.g., polyposis of the colon). Fortunately, the population of dominant gene carriers which predispose to cancer is small, because virtually every gene carrier will acquire the cancer in question. These dominant genes are responsible for a relatively small fraction of adult cancer; it is more important in children (e.g., retinoblastoma). The authors conclude that all tumors follow

at least two events: the first may be mutational (germinal and somatic); the second event is somatic and may be mutational. In addition, any effort to identify high risk cancer groups must take into account the genetic heterogeneity of the study population and the influence of environmental carcinogens. (7 references)

4813 THE DISCRETE PHASES OF THE CELL CYCLE: AUTORADIOGRAPHIC, PHYSICAL, AND CHEMICAL EVIDENCES. (Eng.) Nicolini, C. (Temple Univ. Health Sciences Center, Philadelphia, Pa. 19140). *J. Natl. Cancer Inst.* 55(4):821-826; 1975.

The discrete phases of the cell cycle are assessed using autoradiographic, physical and chemical procedures. Recently the discrete model of the cell cycle, described as a series of metabolic progressions through four distinct phases, has been challenged by a few curves of percent labeled mitoses (PLM) and related autoradiographic data, which have been questionably interpreted in terms of a continuous cell cycle model. In autoradiographical studies, background technical contributions are 5- or 6-fold and are functions of the time exposure and/or the magnitude of the [³H]-thymidine pulse. Background corrections are applied by the arbitrary setting of a threshold grain count below which a cell is treated as nonlabeled. The setting is artificial and misleading. The physical and chemical procedures reveal evidence of a discrete cell cycle as opposed to some autoradiographic studies. The discrete cell cycle is based on quantitative analysis, on automated image analysis, on circular dichroism and dye binding studies, on biochemical analysis and on laser microfluorometry. The concept of discrete cell cycle through which cells proceed stochastically with certain log-normal distributions is well supported. Only through the development of new techniques and the characterization of additional independent physical-chemical parameters of the cell will it be possible to further elucidate the mechanism of growth during the cell cycle. (50 references)

4814 REGULATION OF MEMBRANE CHANGES, DIFFERENTIATION, AND MALIGNANCY IN CARCINOGENESIS. (Eng.) Sachs, L. (Weizmann Inst. Science, Rehovot, Israel). *Harvey Lect.* 68:1-35; 1974.

Studies on the regulation of growth and differentiation in normal and malignant cells, through the development and use of *in vitro* systems, are summarized. Using lectins as probes, the changes in cell regulation produced by malignant cell transformation could be associated with changes in the cell surface. Experiments with concanavalin A (Con A) have shown induced agglutinability of transformed cells, temperature-sensitive activity, the distribution and mobility of Con A binding sites, and Con A binding-induced inhibition of cell multiplication. Various other lectins have also been employed, and have shown the significance of changes in the dynamics of specific surface membrane sites in the control of growth and differentiation. Studies on the mechanism of such growth and differentiation, utilizing a tissue cul-

ture system and a tissue culture cloning assay, have indicated that the protein macrophage and granulocyte inducer (MGI) is required for the differentiation of normal granulocytes and macrophages. MGI is produced *in vitro* by various normal and neoplastic cells, and can be obtained also from *in vivo* sources; it has been utilized in illustrating the heritability of the D⁺ and D⁻ properties in myeloid leukemic cells. Studies on the reversion of the malignant phenotype have revealed a hereditary reversion to a phenotype with normal growth control found with sarcoma cells transformed with tumor viruses, chemical carcinogens, and X-irradiation. Such reversion is not associated with a loss of the viral genome; furthermore, induction of normal differentiation occurs in cells without the normal diploid genotype. Results of studies on reversion, re-reversion, the lack of the normal diploid chromosome complement in revertants, and the association of reversion with changes in the total chromosome number suggest a model for the genetic control of malignancy and cell transformation. The model is based on the assumption that a balance exists between genes for expression and suppression of malignancy. It suggests a mechanism of carcinogenicity, and is supported by chromosome analyses. (126 references)

4815 REGULATION OF GROWTH AND DIFFERENTIATION IN NORMAL AND TUMOR CELLS. (Ger.) Sachs, L. (Akademie der Wissenschaften und der Literatur, Mainz, West Germany). *Akad. Wiss. Lit. Mainz Math. Naturwiss., Kl. Karl-August-Forster-Lect.* 7:9-28; 1974.

Recent cytobiological findings on growth regulation and differentiation in normal and tumor cells are discussed with special regard to cell transformations by DNA tumor virus. Experiments on DNA tumor virus-transformed fibroblasts with concanavalin A and bivalent metal ions revealed the particular significance of the cell surface structure for cell proliferation. The surface of transformed cells has certain structures which are masked in normal cells, but which become exposed during transformation by different carcinogens. Differences are observed between normal and transformed cells in the topographic arrangement of the carbohydrate-containing bond sites. While normal golden hamster cells contain 44 chromosomes, transformed cells contain 44 or 45 chromosomes, and reconverted cells have a chromosome count of 75, 76, 77, or 78, which indicates that the reversion of tumor cells to normal cells does not imply a reversion to normal genotype. The findings indicate that the ability of normal proliferation regulation is dependent on certain genetic factors localized on the chromosomes. The equilibrium between expressor and suppressor genes is disturbed in transformed cells, either due to the increase in expressor genes or to a loss of suppressor genes. The increase in certain chromosome groups with increasing degree of malignancy indicates a correlation between the latter and the chromosome count. The surface changes observed in transformed cells are responsible for the altered proliferation control, and these surface changes have a genetic basis. The reversion to normal cell is believed to involve a shift in the genetic equilibrium toward genes suppressing the expression of the virus information.

- 4816 NERVE GROWTH FACTOR: STRUCTURE AND MECHANISM OF ACTION. (Eng.) Hogue-Angeletti, R. A. (The Inst. Cancer Res., Philadelphia, Pa.); Bradshaw, R. A.; Frazier, W. A. *Adv. Metab. Disord.* 8:285-299; 1975.

The structure, biological function, and mechanism of action of nerve growth factor, first identified as a soluble factor released from certain tumors, are reviewed. Nerve growth factor was purified to homogeneity from the submaxillary gland of the adult male mouse and from the venom of the cobra *Naja naja*. The proteins from these two sources are quite similar in amino acid sequence having identical amino acid residues in about 65% of the positions in their sequences. When the structure of nerve growth factor was compared with those of better understood proteins, it showed a marked similarity to proinsulin at the primary level as well as in elements of secondary and tertiary structure. A comparison of the biological functions of insulin and nerve growth factor showed that both proteins elicit a positive pleiotypic response, in which nearly all anabolic and energy-yielding processes are stimulated and maintained. To determine whether nerve growth factor elicits its biological response through interaction with a receptor on the surface membrane of responsive peripheral neurons, two lines of experimentation were undertaken: (a) The existence of such a receptor was investigated with insolubilized derivatives of nerve growth factor; (b) the properties of the binding of ^{125}I -nerve growth factor to responsive cells was studied. Specific binding of ^{125}I -nerve growth factor was found in whole cell and membrane preparations of dorsal root and sympathetic ganglia of chick embryo, rat, rabbit, and dog and also in embryonic and adult brain. These nerve growth factor receptors in the CNS have been found primarily in synaptic membranes, suggesting a role in the development and maintenance of functional synaptic contacts. The nerve growth factor binding sites are primarily on the cells of the organs themselves, not on sympathetic nerve terminals within the tissues. The function of these receptors on peripheral organs is not yet understood, but they suggest that nerve growth factor may function in the development of specific connections during synaptogenesis in the periphery as well. (38 references)

- 4817 TUMOR PROTEOLIPIDS. (Eng.) Skipski, V. P. (Sloan-Kettering Inst. for Cancer Res., Walker Lab., 145 Boston Post Road, Rye, N. Y. 10580); Barclay, M.; Archibald, F. M.; Stock, C. C. *Prog. Biochem. Pharmacol.* 10:112-134; 1975.

The classification, isolation, and chemical analysis of two neoproteolipids (NPL), NPL-W and NPL-S, are discussed. Studies on different transplanted animal tumors, chemically induced tumors, and spontaneously originated animal and human tumors reveal measurable quantities of NPL in all tumors; the predominance type of NPL is not determined by species-specificity or tumor origin. NPL-W has a chemical composition of 8-11% polypeptides, 25-31% fatty acids, 10-14% sphingosine bases, 40-45% monosaccharides, plus small quantities of free and esterified chole-

sterol and inorganic phosphorus. The patterns suggest that NPL-W is a neutral glycosphingolipid complex with some associated phospholipids and neutral lipids. Use of four different thin-layer chromatography systems reveals little or no NPL-W present in most tissues or organs from normal rats, and highest NPL-W quantities in tumor tissues, averaging 1.09% of total lipids extracts. Further results show that blood plasma/serum from Walker carcinoma 256-bearing rats contains 31-147 $\mu\text{g}/100\text{ mg}$ NPL-W, whereas it is generally absent in blood plasma/serum of normal rats. NPL-S, isolated from mouse sarcoma 180 and rat Morris hepatoma 5123tc by silicic acid column chromatography, also contains similar proteins to NPL-W; however, major differences in the carbohydrate fractions of NPL-S and NPL-W are noted, indicating the participation of different glycosphingolipids. Lipid extraction of whole blood serum from cancer patients and normal control subjects detects no neoproteolipids in 17 normal control patients. However, neoproteolipids are detected in lipid extracts from high-density lipoproteins in 20 of 23 cancer patients tested. NPL-S was specifically determined in a breast carcinoma and a leiomyosarcoma. The composition of neoproteolipids, whose basic components are neutral glycosphingolipids or gangliosides, suggests that the appearance or accumulation of those complexes is probably directly related to altered glycosphingolipid metabolism of malignancy. (62 references)

- 4818 STEROLS AND OTHER LIPIDS IN TUMORS OF THE NERVOUS SYSTEM. (Eng.) Weiss, J. F. (New York Univ. Medical Center, 550 First Ave., New York, N.Y. 10016). *Prog. Biochem. Pharmacol.* 10:227-268; 1975.

Differences in the lipid composition of tumors of the nervous system and normal tissue are comparatively reviewed. Studies of developmental changes in neural lipids in which the major and minor phospholipid quantities and patterns in the developing and mature brain have been determined are discussed. The rate and pattern of sterol synthesis is likewise discussed, as is the varying desmosterol accumulations in the brain, CNS, and peripheral nervous system. Increased quantities of cholesterol esters have been found in the brain during various stages of development, and the effect of various hypocholesterolemic agents on the developing nervous system is discussed. Human tumors of the nervous system are classified into neuroectodermal and mesenchymal groupings. Changes in total lipid content, lipid classes, neutral lipids, and fatty acid composition occurring in the major types of brain tumors are discussed. Findings on the sterol composition and synthesis, phospholipid synthesis, and glycolipid composition of the brain tumors are also presented. An evaluation of the possibilities for lipid analysis, current procedures, and drawbacks of cerebrospinal fluid (CSF) analysis reveals noteworthy differences between normal CSF lipids and blood lipids, increased CSF β -lipoproteins concurring with brain tumors, and the diagnostic use of triparanol in augmenting CSF desmosterol. Numerous models for brain tumor research are presented; intracranial tumors are induced in experimental animals by onco-

genic viruses, carcinogen implantation, and resorptive carcinogens (especially ethylnitrosourea and methylnitrosourea). The sterol metabolism, desmosterol content, and cholesterol content of nitrosourea-induced tumors is discussed at length. The lipid composition, sterol metabolism, and effects of drugs on transplanted tumors are also noted. Tissue culture studies of human and experimental brain tumors have also provided insights into the lipid metabolism, sterol composition, desmosterol accumulation, and effects of hypocholesteremic agents. While the relationship between increased desmosterol in nervous system tumors and the neoplastic process is not clear, the change in the sterol composition and the ability to modify tumor sterol synthesis and composition by the administration of drugs is suggested to have a diagnostic or chemotherapeutic value. (137 references)

- 4819 FUCOLIPIDS AND BLOOD GROUP GLYCOLIPIDS IN NORMAL AND TUMOR TISSUE. (Eng.) Hakomori, S. (Sch. Medicine, Univ. Washington, Seattle, Wash. 98195). *Prog. Biochem. Pharmacol.* 10:167-196; 1975).

The demonstration of fucolipid changes associated with malignant transformation and their enzymatic basis are reviewed. Fucolipids, a new glycosphingolipid class containing fucose at the nonreducing terminal, are very potent antigens and are the blood group haptens of RBC membranes. Numerous studies on the blood group haptens of human RBC membrane are cited; these have demonstrated the presence of multiple blood group active fucolipids and have enabled the characterization of the active component and variants of blood group H-active glycolipids, A-active glycolipids, and B-fucolipids. Lewis-active factors of RBC are fucolipids acquired from serum, although the origin of the serum Lewis fucolipids is unknown. Relatively large quantities of fucolipids are found in gastrointestinal mucosa; fucolipids have been isolated and characterized from dog, porcine, feline, and rat intestines, and from hog stomach mucosa. It is probable that glandular epithelial tissues might contain fucolipids in higher concentrations than in mesenchymal organs. Fucolipids constitute an essential part of membrane-bound surface antigens with blood group A, B, M, and Lewis specificities; the change of blood group antigen associated with malignancy is discussed in detail. The deletion or decrease of blood group A and B antigens, and corresponding chemical changes, have been observed in several tumors. In extensive immunohistological studies, ABH isoantigens have been detected in normal tissues. Diminished or deleted A and B reactivities have been detectable at a very early stage of transformation, and blocked synthesis of A and B determinants has been demonstrated in various transformed cells *in vitro*. Although the Lewis antigen activities show some inconsistency, accumulation of a fucose-containing glycosphingolipid and the co-presence of Le^a and Le^b glycolipids have been found in some human adenocarcinomas. The presence of incompatible blood group antigens in human tumors is described. A clear change of fucolipid class in oncornavirus-transformed tissue culture cells has been unequivocally demonstrated. It is suggested that such fucolipid change may represent

altered antigenicity and various functional changes

- 4820 CYCLIC PURINE NUCLEOTIDES (3',5'-ADENOSINE MONOPHOSPHATE AND 3',5'-GUANOSINE MONOPHOSPHATE) AS REGULATORY FACTORS OF THE PROLIFERATION AND DIFFERENTIATION OF HEMOPOIETIC CELLS. (Rus.) Fedorov, N. A. (Central Inst. Hematol. Blood Transf., Min. Publ. Health U.S.S.R., Moscow, U.S.S.R.). *Usp. Sovrem. Biol.* 79(2):225-240; 1975.

Studies on the cyclic purine nucleotides 3',5'-adenosine monophosphate (cAMP) and 3',5'-guanosine monophosphate (cGMP) as regulatory factors of the proliferation and differentiation of bone marrow cells, thymocytes and lymphocytes in humans and animals are reviewed. Both compounds play a trigger role in the mitosis of lymphocytes. Exogenous cAMP and dibutyryl-cAMP inhibit the growth of tumor and leukemia cells both *in vitro* and *in vivo*. Normalization of mouse neuroblastoma cells and of human astrocytoma and neuroblastoma cells by endogenous cAMP and exogenous dibutyryl-cAMP has been observed. Treatment with cAMP fully suppressed the tumor induction ability of human KB tumor cells in hamsters. Malignant cells are characterized by low cAMP levels and increased susceptibility to exogenous cAMP or to substances which stimulate its intracellular synthesis. Tumorous and leukemia transformations appear to be linked with changes in the adenyl cyclase-cAMP phosphodiesterase system which regulates the intracellular cAMP level. In contrast to cAMP, cGMP stimulates the cell proliferation, and inhibits cell differentiation. (100 references)

- 4821 ALTERED PATTERNS OF AMINOACYL-tRNA SYNTHETASES IN TUMORS (AND THEIR POSSIBLE SIGNIFICANCE). (Eng.) Del Monte, U. (Inst. General Pathology, Univ. Florence, Italy). *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 89-94.

Studies on the activities of aminoacyl-tRNA synthetases in hepatomas are described. Most studies have employed enzyme fractions obtained from post-microsomal supernatants by gel filtration through Sephadex G75. A tabulation of the activity of aminoacyl-tRNA synthetases in normal liver and in hepatomas indicates that: (a) the total aminoacyl-tRNA synthetase activities of the slow-growing, well-differentiated Morris hepatomas (5123c and 7793) are rather close to the activity of the liver, (b) the total activity of the fast-growing anaplastic Yoshida hepatoma (AH130) is about three times higher, and (c) all three hepatomas have aminoacyl-tRNA patterns different from that of liver. The apparent K_m for five amino acids of aminoacyl-tRNA synthetases from liver and hepatomas 7793 and AH130 are also tabulated. The results suggest that molecular changes of aminoacyl-tRNA synthetases are rather uncommon in hepatomas. Studies of enzyme patterns have revealed significant correlation for several enzyme activities; by means of a multivariate (factor) analysis, the enzymes are tentatively grouped on the bases of their observed interrelationships.

Based on the data of 51 patterns, a factor analysis of aminoacyl-tRNA synthetase activities for the single amino acids is then presented. The analysis suggests that some enzymes (e.g. histidyl- and alanyl-tRNA synthetase) behave as if they were under specific controls, independent from each other and from mechanism(s) controlling the majority of the other synthetases. However, leucyl- and isoleucyl-tRNA appear to share another distinct control mechanism. Recent evidence also indicates that mammalian aminoacyl-tRNA synthetases may exist in a complex with each other, with ribosomes, and with membranes. It is hypothesized that because of their key position in the translation machinery, changes in the abundance of aminoacyl-tRNA synthetases are associated with metabolic regulation and cellular differentiation. (19 references)

- 4822 TESTING OF EXOGENOUS SUBSTANCES FOR MUTAGENICITY (Ger.) Vogel, F. (Inst. Anthropol. Hum. Genet., Univ. Heidelberg, West Germany); Rohrborn, G.; Hansmann, I. *Arzneim Forsch* 24(10): 1665-1677; 1974. (89 references)

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- 4824 AFLATOXINS IN FOOD. (Eng.) Anonymous. *Chemistry* 48(2):20; 1975. (2 references)

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- 4826 BENZENE RINGS AND THE BLADDER. (Eng.) Carter, R. L. (Royal Cancer Hosp., Fulham Road, London SW3 6JB, England). *Lancet* 2(7934):553; 1975. (14 References)

- 4827 INTAKE OF POLYNUCLEAR HYDROCARBONS. (Eng.) Shabad, L. M. (Inst. Experimental and Clinical Oncology, Acad. Medical Sciences U.S.S.R., Moscow). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 48-49. (1 reference)

- 4828 HYDROCARBON DERIVATIVE-NUCLEIC ACID INTERACTIONS IN CHEMICAL CARCINOGENESIS. (Eng.) Dipple, A. (Royal Cancer Hosp., Fulham Rd., London SW3 6JB, U.K.). *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.;

Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 41-46. (64 References)

- 4829 TOXICITY OF VINYL CHLORIDE-POLYVINYL CHLORIDE: DISCUSSION PAPER. (Eng.) Doll, R. (Oxford Univ., England). *Ann. N.Y. Acad. Sci.* 246:320-321; 1975. (No references)

- 4830 A RADIOBIOLOGICAL ASSESSMENT OF THE SPATIAL DISTRIBUTION OF RADIATION DOSE FROM INHALED PLUTONIUM. (Eng.) Bair, W. J. (Atomic Energy Commission, Washington, D.C.); Richmond, C. R.; Wachholz, B. W. 46 pp., 1974. [available through National Technical Information Services, Washington D.C. Document No. WASH-1320]

- 4831 PLUTONIUM AND OTHER TRANSURANIUM ELEMENTS: SOURCES, ENVIRONMENTAL DISTRIBUTION AND BIOMEDICAL EFFECTS. A COMPILATION OF TESTIMONY PRESENTED BEFORE AN ENVIRONMENTAL PROTECTION AGENCY HEARING BOARD, DECEMBER 10-11, 1974, AT WASHINGTON D.C. (Eng.) Wachholz, B. W. (Atomic Energy Commission, Washington D.C.); Liverman, J. L.; Yoder, R. E., Jr.; Wrenn, M. E.; Bennett, B. G. 332 pp., 1974. [available through National Technical Information Services, Washington D.C. Document No. WASH-1359].

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- 4833 RNA PROCESSING AND RNA TUMOR VIRUS ORIGIN AND EVOLUTION. RNA TUMOR VIRUS GENOMES MAY ORIGINATE FROM CELL DNA VIA AN ALTERNATIVE MODE OF RNA PROCESSING CALLED PARAPROCESSING. (Eng.) Gillespie, D. (Natl. Cancer Inst., Bethesda, Md.); Gallo, R. C. *Science* 188(4190):802-811; 1975. (74 references)

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- 4839 IMMUNOLOGY AND IMMUNOTHERAPY OF ACUTE CHILDHOOD LEUKEMIA. (Eng.) Sokal, J. E. (Dept. Medicine B, Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14263). *Prog. Clin. Biol. Res.* 4:53-63; 1975. (16 references)
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- 4841 ACUTE LYMPHOID LEUKEMIAS: CLINICAL AND CYTOLOGICAL FEATURES. (Eng.) Mathe, G. (Institut de Cancerologie et d'Immunogenetique, Groupe Hospitalier Paul-Brousse, Avenue Paul-Vaillant-Couturier, F-94800 Villejuif, France); Amiel, J.-L.; Schwarzenberg, L. *Mod. Probl. Paediatr.* 16:1-38; 1975. (128 References)
- 4842 LYMPHATICS, LYMPHEDEMA AND LYMPHANGIOSARCOMA. (Eng.) Deigert, F. A. (Billings, Montana). *Rocky Mt. Med. J.* 72(5):210-213; 1975. (7 references)
- 4843 INTRAVASCULAR EVENTS IN CANCER DESSEMINATION: THE ADHESION OF CELLS TO VASCULAR ENDOTHELIUM [abstract]. (Eng.) Atherton, A. (Imp. Cancer Res. Fund, London, England). *Eur. J. Cancer* 11(1):33-34; 1975. (No references)
- 4844 EPIDEMIOLOGY OF CARCINOMA OF THE UTERINE CERVIX. (Eng.) Koss, L. G. (Albert Einstein Coll. Medicine, 111 E. 210th St., Bronx, N.Y. 10467). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 307-313. (35 references)
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- 4846 MESOTHELIOMAS. (Eng.) Wagner, J. C. (Llandough Hosp., Penarth, S. Glamorgan, Wales, U.K.). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 323-326. (8 references)
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- 4849 ESTIMATION OF RISKS DUE TO ENVIRONMENTAL CARCINOGENESIS. (Eng.) Cranmer, M. F. (Nat'l. Cent. Toxicol. Res., Jefferson, Arkansas). *Proc. Am. Assoc. Cancer Res.* 16:208; 1975. (No references)
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- 4852 CANDIDATE DRUGS FOR CARCINOGENIC PROPERTY STUDIES: PROCEDURES. (Eng.) Rall, D. P. (Nat'l. Inst. Environ. Health Sci., Res. Triangle Park, N. C.). *J. Clin. Pharmacol.* 15(1):1-4; 1975.

The problem associated with the potential carcinogenicity of new and old drugs is discussed and procedures for minimizing this problem are suggested. It is likely that the third major drug regulatory crisis within the past few decades is developing now over concern for the problem of drug-induced carcinogenesis. A greater carcinogenic risk might be permitted in unique and curative drugs than in those which simply ameliorate symptoms or have adequate substitutes. Serious damage to the drug development process would be caused by demanding a two-yr feeding study prior to initiating the first clinical investigation of a new drug. There are two ways in which the risk can be reduced to an acceptable level while preserving the drug development process: (1) the utilization of simple, quick, and extensive *in vitro* mutagenesis assays which would indicate a high likelihood of carcinogenic activity. A positive test would indicate the need for a two-yr test before proceeding with the development of the agent in question; and (2) the use of standard toxicology studies to indicate drugs which have a potential to interact with DNA or to interfere with cell division. Promising new drugs as well as drugs already on the market should then be evaluated in classic lifetime rodent studies for carcinogenicity, using tests which are relevant to the clinical use of the drug. Finally, a system is needed to study the long-term effects of drugs in clinical usage. This would involve the establishment of an advanced adverse drug reaction surveillance system including a record linkage system which would allow follow-up of patients who have been exposed to the drugs in question. In this way, the output of valuable life-saving new drugs could be increased while minimizing the danger that the drugs themselves would cause damage to the patient.

- 4853 SEQUENTIAL HISTOLOGICAL AND HISTOCHEMICAL STUDY OF THE RAT LIVER DURING AFLATOXIN B₁-INDUCED CARCINOGENESIS. (Eng.) Kalengayi, M. R. (Laboratorium voor Histochemie en Cytochemie, Departement Medische Navorsing, Fakulteit Geneeskunde, Katholieke Universiteit Leuven, B 3000 Leuven, Belgium); Desmet, V. J. *Cancer Res.* 35(10):2845-2852; 1975.

Male Wistar rats were given 50 µg of aflatoxin B₁ twice a week for four weeks and thereafter 75 µg twice a week for ten weeks. Their livers were investigated histologically and histochemically for glycogen, RNA, fat, alkaline and acid phosphatases, adenosine triphosphatase, 5'-nucleotidase, glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, succinic dehydrogenase, and alkaline and acid nucleases. No significant lesions occurred before 15 wk. During this period, the liver was histochemically unchanged except for a periportal decrease of alkaline phosphatase and adenosine triphosphatase. Scattered hepatocytes with a strong glucose-6-phosphatase activity appeared. These changes represent toxic effects of aflatoxin B₁ and are irrelevant to

carcinogenesis. From 15 wk onward, three types of liver cell hyperplasia foci and nodules developed. Histologically, and with respect to glycogen, fat, and RNA content, only two of these types were considered as potential precursors of hepatocarcinomas. However, all types exhibited a decrease or absence of the enzymes studied. Both histological and histochemical changes stressed the complex heterogeneity existing between and within hepatic foci and nodules. From 11 mo on, hepatocarcinomas developed. The tumors disclosed similar histochemical changes. This similarity further supports the "precarcinomatous" nature of hyperplastic foci and nodules. It appears that focal changes in surface as well as in cytoplasmic and nuclear enzymes are intimately and very early linked to the carcinogenic process. Whether they are fundamental or only represent an epiphenomenon remains unclear.

- 4854 CEREBRAL GRANULAR CELL TUMOR IN THE RAT AFTER INTRAPERITONEAL APPLICATION OF AFLATOXIN B₁ DURING PREGNANCY. (Ger.) Tschahargane, C. (D-6900 Heidelberg, Postfach 104340, West Germany); Goerttler, K.; Ule, G.; Volk, B. *Acta Neuropathol. (Berl.)* 32(4):281-285; 1975.

A granular cell tumor measuring 5 x 4 x 4 mm found in the right frontal pole of the cerebrum in a rat that had been administered aflatoxin B₁ (0.5 mg/kg/day, ip) between the 18th and 21st days of pregnancy 12 mo before spontaneous death due to the tumor was described. The tumor originated from the leptomeninges. The light and electron-microscopic findings and the nucleic acid concentrations justify a comparison with the Abrikossoff tumor. The protein content of the granules of the tumor cells was higher than that known for granular cell myoblastoma of man. No tumor was found in other organs. The offspring of the aflatoxin B₁-treated female was normal. The granulocytic tumor, possibly induced by aflatoxin B₁ in the rat, may serve as an experimental model for the study of this rare neoplasm.

- 4855 THE EFFECTS OF O-ACETYLSTERIGMATOCYSTIN AND RELATED COMPOUNDS ON RAT LIVER AND CULTURED CHICKEN EMBRYONAL LIVER CELLS. (Eng.) Terao, K. (Res. Inst. for Chemobiodynamics, Chiba Univ., Izumi-cho, Narashino, Chiba 275 Japan); Takano, M.; Yamazaki, M. *Chem. Biol. Interact.* 11(6):507-522; 1975.

Fine structural nucleolar changes induced in rat liver and primary tissue culture cells from 10-day-old chicken embryonal liver by O-acetylsterigmatocystin (AcO-stg), related compounds and aflatoxin B₁ were compared. Male Wistar rats were given a single ip injection of sterigmatocystin (stg), AcO-stg, and aflatoxin B₁. Three days after the injection of 15 mg/kg of stg, sporadic single cell necrosis was observed in rat liver, whereas rats treated with 8 mg/kg AcO-stg or more, and 3 mg/kg of aflatoxin B₁ showed massive liver necrosis. Acetylation resulted in a marked increase in solubility in polar organic solvents. This increased solubility could thus play an important role in determining toxicity. Treat-

ment with the compounds with an unsaturated $\Delta^{1,2}$ -furobenzofuran ring system, such as AcO-stg, demethyl-diacyl-sterigmatocystin (deMe-diAc-stg), and aflatoxin B₁, resulted in nucleolar segregation and fragmentation of primary culture cells. Both parenchymal and mesenchymal cells in culture were susceptible to AcO-stg and deMe-diAc-stg, while the mesenchymal cells were more resistant to aflatoxin B₁ than the hepatocytes. The inhibition of RNA synthesis in both cell types, as determined by radioautography, was in accordance with the electron-microscopic observations. Acetyldihydrosterigmatocystin, a saturated $\Delta^{1,2}$ -furobenzofuran ring compound, was less toxic to primary tissue culture cells. The acetylation of stg may be a useful method for analyzing the toxicity of stg, a potentially potent carcinogen.

4856 THE EFFECT OF VARIABLE SERUM FACTORS AND CLONAL MORPHOLOGY ON THE ABILITY TO DETECT HYPOXANTHINE GUANINE PHOSPHORIBOSYL TRANSFERASE (HPRT) DEFICIENT VARIANTS IN CULTURED CHINESE HAMSTER CELLS. (Eng.) Newbold, R. F. (Inst. Cancer Res., Chester Beatty Res. Inst., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks. HP8 4SP England); Brookes, P.; Arlett, C. F.; Bridges, B. A.; Dean, B. *Mutat. Res.* 30(1):143-148; 1975.

Deviations from the normal response in variants resistant to 8-azaguanine in the V79 Chinese hamster cell line are described, and remedial action is suggested. Deviations from the normal response are of two types. The first is a lack of response of azaguanine-sensitive cells to the selective agent, and the second is related to changes in apparent mutability. Variation in the response to the selective agent is invariably associated, with the introduction of a new batch of fetal calf serum. Subsequent dialysis of such sera has resulted in normal 8-azaguanine sensitivity of cells in repeat experiments. It is suggested that the effect is due to the presence of purines sufficient in concentration to compete effectively with 8-azaguanine for hypoxanthine guanine phosphoribosyl. The appropriate remedial action is either to raise the concentration of 8-azaguanine or to dialyze the serum. The use of 8-azaguanine at a final concentration of 30 μ g/ml has given reliable results. The second type of change is manifest as a failure to demonstrate mutation induction following treatment with a known mutagen, which has previously been shown to be effective. It is suggested that a cell ultimately capable of giving rise to genetically 8-azaguanine-resistant progeny has, at the hypoxanthine guanine phosphoribosyl locus, a mutation already existing in one DNA strand. At the time of selection, most potentially 8-azaguanine-resistant clones will contain a mixture of resistant and sensitive cells. Unless these cells move apart during clonal growth, metabolic cooperation must be expected, and the mutant cell will tend to become phenotypically 8-azaguanine-sensitive, unable to form visible colonies in the presence of the selective agent. Efficiency of selection has been improved by lowering the plating density to between 1×10^4 and 1×10^5 viable cells per 9-cm dish. It may be possible to overcome metabolic cooperation at the intra-clone level by allowing expression to occur in suspension culture or by dispersing the

cells in a clone by respreading before adding the selective agent.

4857 THE INTERACTION OF NATURAL TETRA-AZACYCLOPENTAZULENE DYES WITH DNA AND THEIR EFFECTS ON THE DNA AND RNA POLYMERASE REACTIONS. (Eng.) Quadrifoglio, F. (*Natl. Cancer Inst., Via Venezian 1, 20133-Milan, Italy); Crescenzi, V.; Protta, G.; Cariello, L.; Di Marco, A.; Zunino, * *F. Chem. Biol. Interact.* 11(2):91-99; 1975.

The interaction of two natural tetra-azacyclopentazulene dyes, zoanthoxanthin and its 3-norderivative, with native calf thymus DNA in 0.01 M acetate buffer (pH 5.0) was studied by means of microcalorimetric, viscosimetric, and spectroscopic measurements. Zoanthoxanthin was isolated from *Parazoanthus axinellae*, and 3-norzoanthoxanthin was preferentially obtained from zoanthoxanthin itself by selective demethylation at N-3. The influence of these dyes on the template capacity of DNA in the *in vitro* synthesis of nucleic acids was also determined using enzyme assays for *Escherichia coli* DNA polymerase and RNA polymerase and for rat liver DNA polymerase. The intrinsic viscosity of DNA increased with increasing r (molar ratio between the bound dye and the DNA-P) by about 40-50% with respect to the intrinsic viscosity of DNA alone up to $r = 0.15$, and then decreased on further addition of either dye. The heat of interaction in kcal/mole of total dye in solution of either dye gave a positive result throughout the range of r values considered and exhibited a discontinuous trend with increasing r . Up to $r = 0.12$, the heat of interaction was constant and amounted to 3.1 kcal/mole for zoanthoxanthin and 3.4 kcal/mole for 3-norzoanthoxanthin. The dyes selectively inhibited DNA synthesis. No appreciable inhibitory effect upon *E. coli* RNA polymerase was observed. Both compounds had a greater inhibitory effect on rat liver high molecular weight DNA polymerase than on *E. coli* DNA polymerase I. Zoanthoxanthin was a more effective inhibitor than 3-norzoanthoxanthin. It is concluded that these results are consistent with the hypothesis of an intercalative-type binding. Comparison of the calorimetric studies, however, indicates that the changes in enthalpy associated with the interaction of these dyes with DNA are, in absolute value, significantly lower than those found with known intercalating agents (daunomycin, ethidium bromide). It is suggested that this might be attributed to the slight departures from planarity of the dye molecules and/or to other steric effects. Alternatively, intercalation may be complete but the interactions between the bases and the azacyclopentazulene rings may not proceed as efficiently as those with other intercalating compounds because of the particular electronic structure of these dyes.

4858 NUCLEAR PROTEINS OF RAT LIVER AND OF AN AMINOAZO-DYE-INDUCED HEPATOMA. (Eng.) Fujitani, H. (Univ. Texas Medical Branch, Galveston, Tex. 77550); Holoubek, V. *Int. J. Cancer* 16(2):329-338; 1975.

The protein composition of the chromatin and of the

nuclear sap proteins of normal female Holtzman rat liver and of Chang's hepatoma were compared. Nuclear proteins of liver and ascites hepatoma were fractionated by extraction in solutions of different salt concentration and analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis. The difference between the electrophorograms of the different fractions of nuclear proteins isolated from liver and from hepatoma was found in the bands which had the same electrophoretic mobility as the main proteins of informofers, and were extracted from nuclei at salt concentrations which extracted informofers. These changes in the electrophoretic patterns of proteins with the solubility and mobility of the proteins of informofers could be related to the defective processing of heterogeneous nuclear RNA in the hepatoma. In addition, the identity of electrophorograms of nuclear proteins isolated from liver and from hepatoma and the identity of most bands in the electrophorograms of nuclear proteins that were soluble in 0.35 M NaCl and chromosomal proteins that were not soluble at this concentration support the notion that these nonhistone nuclear proteins that can be identified as the major bands in electrophorograms of chromosomal proteins are not the specific regulators of gene expression.

- 4859 THE CARCINOGENIC AND ELECTROPHILIC ACTIVITIES OF *N*-BENZOYLOXY DERIVATIVES OF *N*-METHYL-4-AMINOAZOBENZENE AND RELATED DYES. (Eng.) Wislocki, P. G. (Univ. Wisconsin Med. Cent., Madison); Miller, J. A.; Miller, E. C. *Cancer Res.* 35(4):880-885; 1975.

The *N*-benzoyloxy derivatives of *N*-methyl-4-aminoazobenzene (MAB), its 4'-methyl and 4'-ethyl derivatives, and *N*-ethyl-4-aminoazobenzene were synthesized for comparison of their structure, carcinogenic activities, and reactivities with nucleophilic reagents. These four dyes had similar degrees of nonenzymatic reactivity with methionine and guanosine at neutral pH. Each induced sarcomas at the site of s.c. injection in male, random-bred CD rats. *N*-benzoyloxy-*N*-methyl-4-aminoazobenzene was considerably more carcinogenic and more stable in neutral lipid. This stability may have contributed to its greater carcinogenic activity. Neither the electrophilic reactivities nor the s.c. carcinogenicities of these dyes paralleled the hepatocarcinogenic activities of the parent dyes. The results suggest that an ester of *N*-hydroxy-MAB or a metabolite with similar electrophilic reactivity is an ultimate reactive form of MAB and that *N*-benzoyloxy-MAB may serve as a prototype for an ultimate carcinogenic metabolite of MAB in rat liver. It was also hypothesized that the MAB homologs might differ in hepatic carcinogenicity due to differences in the extent to which they are *N*-hydroxylated or to which their *N*-hydroxy derivatives are esterified in the liver, or both.

- 4860 MODIFICATION OF TOXIC LIVER INJURY IN THE RAT: II. PROTECTIVE EFFECT OF CYCLOHEXIMIDE ON ETHIONINE-INDUCED DAMAGE AND AUTOPROTECTIVE EFFECTS OF HIGH DOSES OF ETHIONINE, 3'-METHYL-4-DIMETHYLAMINOAZABENZENE, AND 2-ACETYLAMINOFLUORENE. (Eng.) Flaks, B. (Dept. Pathology, Univ. Bristol,

Bristol, Great Britain); Nicoll, J. W. *Toxicol. Appl. Pharmacol.* 32(3):603-620; 1975.

The effects of various single po doses of DL-ethionine, with and without accompanying doses of cycloheximide, were investigated in male and female Wistar rats. Groups of six rats received a single ip injection of cycloheximide (1.5 mg/kg) immediately after the DL-ethionine administration; another group received an additional identical dose 5.5 hr after the first. Three animals from each group were killed 24 hr after treatment, and the other three were killed 48 hr after treatment. A single dose of cycloheximide prevented the appearance of hepatic cell damage in DL-ethionine-treated female rats, up to 48 hr. At this time, 2,000 mg/kg DL-ethionine was necessary to induce moderate cytoplasmic vacuolation of the periportal hepatocytes. In the male rat, the two consecutive doses of cycloheximide were necessary to achieve protection. However, very large doses of DL-ethionine (up to 8,000 mg/kg) alone failed to produce the early liver injury that resulted from lower doses, although delayed damage did appear after several days. Similar results were obtained with high doses of 2-acetylaminofluorene (600 mg/kg). Very high doses of 3'-methyl-4-dimethylaminoazobenzene (1,200 mg/kg) failed entirely to induce the periportal hepatic cell lesion which is characteristic of this agent, instead giving rise to minimal centrilobular necrosis and leading to a massive proliferation of bile duct cells within a week.

- 4861 CARCINOGENIC ACTIVITY OF DI- AND TRIFUNCTIONAL α -CHLORO ETHERS AND OF 1,4-DICHLOROBUTENE-2 IN ICR/HA SWISS MICE. (Eng.) Van Duuren, B. L. (New York Univ. Medical Center, New York, N.Y. 10016); Goldschmidt, B. M.; Seidman, I. *Cancer Res.* 35(9):2553-2557; 1975.

Six compounds were tested for carcinogenicity in female ICR/Ha Swiss mice for 502-569 days (depending on length of survival). The compounds tested were: bis-1,2-(chloromethoxy)ethane (Compound I), bis-1,4-(chloromethoxy)butane (Compound II), bis-1,6-(chloromethoxy)hexane (Compound III), bis-1,4-(chloromethoxy)-*p*-xylene (Compound IV), and tris-1,2,3-(chloromethoxy)propane (Compound V). *Trans*-1-4-Dichlorobutene-2 (Compound VI) was tested along with the five α -chloro ethers. For skin application experiments, the dorsal skin was shaved initially and thereafter when necessary. The compounds were applied to the interscapular region three times/wk. Skin lesions were diagnosed as papillomas when they reached 1 mm in diameter and when they persisted for at least 30 days. Compound I produced four papillomas and four squamous carcinomas. Compound IV (0.3 mg in cyclohexane) produced seven papillomas and seven squamous carcinomas plus one undifferentiated malignancy. Compound V gave six papillomas and three squamous carcinomas. The results with compounds I and IV were significant at $P < 0.05$. Compounds were injected sc (0.3 mg in 0.05 ml tricapylin) once weekly in the second experiment. The number of mice with local sarcomas/50 mice treated was nine after treatment with compound I, 11 plus a squamous cell carcinoma after compound IV, and ten plus two

carcinomas at the injection site, after compound V. Three mice of 30 were found to have local sarcomas after sc injection of compound VI. All of these results differed significantly from the controls. In a third experiment, the compound were injected ip once/wk in 0.05 ml of tricaprylin. The number of mice with local sarcomas/30 mice tested was two after compound I (0.3 mg/dose), two after compound IV (0.1 mg/dose), and five after compound V (0.3 mg/dose). Compounds I, IV, and V gave notable tumor incidences by all three routes of administration.

4862 CYTOTOXIC AND ONCOGENIC ACTIVITIES OF 1,1,1-TRICHLORO-2,2-BIS (p-CHLOROPHENYL)-ETHANE AND METABOLITES TO MOUSE EMBRYO CELLS IN CULTURE. (Eng.) Langenbach, R. (Univ. Nebraska Med. Cent., Omaha); Gingell, R. *J. Natl. Cancer Inst.* 54(4):981-983; 1975.

An *in vitro* mouse cell transformation system was used to measure the relative cytotoxic and oncogenic activities of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE), 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (DDD), and bis(p-chlorophenyl)acetic acid (DDA). For plating efficiency (cytotoxicity) determination and transformation (oncogenicity) assay, 200 and 500 malignantly transformable cloned mouse embryo cells, respectively, were seeded in 4 ml medium. Compounds were dissolved in dimethylsulfoxide (DMSO) or 7,12-dimethylbenz(a)anthracene (DMBA) and added 24 hr after seeding. Plating efficiencies were determined in 7-10 days. Transformation was scored six weeks after seeding. C3H mice were irradiated with ^{60}Co for 24 hr before sc inoculation with transformed foci isolated after four passages from cells treated with each compound. After 14 mo of observation, DDD was the most cytotoxic and the most active transforming agent. The foci produced by DDT and its metabolites were equally distributed between types I and II morphologies. On subculture, these cells had 30-50% higher saturation density than did the parent cells, suggesting that focus formation was not due to cytotoxic effects. DMBA type III foci produced tumors in about 50% of inoculations, whereas one tumor resulted from inoculation of three DMBA type II foci. The transformed foci in the mouse embryo system treated with test compounds were nontumorigenic in any inoculated mice and showed low transforming activity. None of these compounds can be designated strongly oncogenic by this assay.

4863 INTERNAL CATALYSIS IN THE REACTION OF N,N,N' -TRIMETHYLETHYLENEDIAMINE WITH PHENYLGLYOXAL HYDRATE TO GIVE N -(2-DIMETHYLAMINOETHYL)- N -METHYLMANDELAMIDE. (Eng.) Hine, J. (Dept. Chemistry, Ohio State Univ., Columbus, Ohio 43210); Fischer, C. D., Jr. *J. Am. Chem. Soc.* 97(22):6513-6521; 1975.

To study the mechanism by which enzymes catalyze the transformation of glyoxal derivatives to α -hydroxy acids, the reaction of N,N,N' -trimethylethylenediamine with phenylglyoxal hydrate was investigated.

The reactions of some simple tertiary and secondary amines (2-methoxy- N -methylethylamine, N -mandeloylpyrrolidine, N -mandeloylmorpholine, N -(2-dimethylaminoethyl)- N -methylmandelamide, N -(α -hydroxyphenyl)pyrrolidine, N -(α -hydroxyphenyl)morpholine, and N -(α -hydroxyphenyl)- N -methyl-2-methoxyethylamine were also studied. The reaction kinetics, acidity constants, equilibrium constants from carbinolamine formation, and products of reactions of phenylglyoxal hydrate with bases were determined. The transformation of phenylglyoxal hydrate to mandelate ions was subject to general base catalysis by trimethylamine. The kinetics of reaction with pyrrolidine, morpholine, and 2-methoxy- N -methylethylamine revealed additional reaction paths, some of which gave amides of mandelic acid. The reaction of N,N,N' -trimethylethylenediamine with phenylglyoxal hydrate proceeded almost entirely by a pathway that was first order in unprotonated amine and first order in electrically neutral hydrate. This reaction, which yields N -(2-dimethylaminoethyl)- N -methylmandelamide as a major product, was about 100 times as fast as would be expected from the results obtained with the other secondary amines. The high rate is believed to result from the reversible formation of the carbinolamine $\text{PhCOCH}(\text{OH})\text{NMeCH}_2\text{CH}_2\text{NMe}_2$, whose dimethylamino group acts as an internal basic catalyst, removing the hydroxylic proton and thus facilitating hydride migration to the carbonyl group *via* a transition state.

4864 HAIR DYES ARE MUTAGENIC: IDENTIFICATION OF A VARIETY OF MUTAGENIC INGREDIENTS. (Eng.) Ames, B. N. (Biochemistry Dept., Univ. California, Berkeley, Calif. 94720); Kammen, H. O.; Yamasaki, E. *Proc. Natl. Acad. Sci. USA* 72(6):2423-2427; 1975.

The mutagenicity of 169 oxidative-type hair dyes was studied using a bacterial test involving *Salmonella typhimurium* strain, TA1538. After addition of test substance to the bacterial cultures, revertant colonies were counted after 48 hr of incubation at 37 C, and spontaneous revertant controls (less than 40 colonies per plate) were subtracted. The results were plotted as dose-response curves, the doses ranging from 0-100 $\mu\text{g}/\text{plate}$. Of the dyes, 150 (89%) were highly mutagenic. Of the 18 components of these dyes, nine were mutagenic by themselves: 2,4-diaminoanisole, 4-nitro-*o*-phenylenediamine, 2-nitro-*p*-phenylenediamine, 2,5-diaminoanisole, 2-amino-5-nitrophenol, *m*-phenylenediamine, *m*-phenylenediamine, *o*-phenylenediamine, 2-amino-4-nitrophenol, and 2,5-diaminotoluene. Three components became strongly mutagenic after oxidation by H_2O_2 : *p*-phenylenediamine, 2,5-diaminotoluene, and 2,5-diaminoanisole; the latter compounds increased revertants by 40-fold. The wide spread use of the mutagenic dyes may be hazardous, in that they may produce human cancers.

4865 CHRONIC TOXICITY, TERATOLOGIC, AND REPRODUCTION STUDIES WITH HAIR DYES. (Eng.) Wernick, T. (*Medical Dept., Bristol-Myers Products, 345 Park Ave., New York, N.Y. 10022); Lanman, B. M.; Fraux, J. L. *Toxicol. Appl. Pharmacol.* 32(3):450-460; 1975.

Potential systemic toxic effects of dyes used in hair colors, which consist mainly of nitrophenylenediamines and nitro-aminophenols and their N-substituted derivatives, were examined in dogs, rats, and rabbits. A composite material representative of a series of commercially available semipermanent hair coloring products was prepared using the highest concentration of each dye and base component present in any formulation of the series. This composite was incorporated into the diet of 18 male and 18 female dogs at concentrations of 0.0, 19.5, and 97.5 mg/kg/day. Each dog was examined daily for two years to assess chronic toxicity. Sixty male and 120 female Sprague-Dawley CD strain rats were also fed the composite in a basal diet at concentrations of 1, 1,950, and 7,800 ppm. In one series of experiments the females received the diet from eight weeks prior to mating through the waning of their litters; the males siring these litters were fed the diets for eight weeks prior to mating and during the mating period. In the second series of experiments, males received the diet for eight weeks prior to and during mating, while the females received the test diets eight weeks prior to mating and during gestation and 21 days of lactation. One female pregnant by each male was killed on day 13 of the pregnancy to obtain information regarding the early stages of gestation. The litters of the other females were examined for live and stillborn pups and gross abnormalities. In a study of the teratologic effects of the composite, 60 male and 60 female virgin CFE rats were mated. The females were fed the composite in the diet from day six through day 15 of gestation at levels of 0, 1,950, and 7,800 ppm. The females were killed on the 19th day of pregnancy and the pups examined for gross, visceral and skeletal abnormalities. The effects of the composite were also studied in 48 artificially inseminated New Zealand White rabbits by daily gavage on days 6-18 of gestation with the composite at doses of 19.5 or 97.5 mg/kg/day. On the 30th day of gestation, the rabbits were killed and the fetuses examined for abnormalities. At the levels of dyes administered, dogs, rats, and rabbits excreted dark blue-brown urine, much the same as the color obtained by adding the composite to urine. In dogs, no adverse effects were attributed to ingestion of the composite. Fertility, gestation, lactation, and viability indices in the rats were similar for the control and experimental groups. Neither rats nor rabbits showed evidence of a teratologic effect. It is concluded that at the levels tested, the composite produced no adverse effects.

- 4866 STUDY OF THE CYTOGENETIC EFFECT OF MEDICINAL DRUGS ON HUMAN CHROMOSOMES *IN VIVO* AND *IN VITRO*. (Rus.) Avedi, L. V. (Inst. Genet. Cytol., Acad. Sci. Belorussian S.S.R., Second Clin. Hosp., Minsk, U.S.S.R.); Kukushkin, I. M.; Kukushkina, L. M. *Dokl. Akad. Nauk B.S.S.R.* 19(8):758-761; 1975.

The cytogenetic action of the drugs fluorethane (FT), succinylcholine chloride (SC) and hexobarbital (HB) used in anesthesiology was studied in human lymphocyte cultures and *in vivo*. Peripheral blood lymphocytes were taken from patients before, immediately and ten days after surgery. When introduced in the mitotic cycle (G1 (24 hr), HB and SC

increased the frequency of spontaneous chromosomal aberrations by 5% and 5.2%, respectively, against 1.1% in the control. When introduced at phase S (40 hr), the effect on the chromosomes was weaker. The combination of the three drugs increased the spontaneous chromosomal aberration frequency to 9.3% at stage G1, and to 8% at stage S. The incidence of spontaneous chromosomal aberrations was 1.2% before surgery, 10% after anesthesia, and 8% 10 days after surgery. Chromatid type aberrations were more frequent *in vitro* than *in vivo*. The findings indicate the cytogenetic effect of HB and SC on human lymphocytes *in vitro* and *in vivo* and the additive effect of HB and SC.

- 4867 EFFECT OF ACTIVATED NITROFURANS ON DNA. (Eng.) Tu, Y. (McMaster Univ. Health Sciences Centre, 1200 Main St. West, Hamilton, Ontario L8S 4J9, Canada); McCalla, D. R. *Biochim. Biophys. Acta* 402(2):142-149; 1975.

The effect of various enzymatically activated nitrofurans (FANFT, nitrofurazone, nitrofuantoin, and AF-2) on *Escherichia coli* DNA was studied *in vivo* and *in vitro*. *In vivo*, minicells were labeled with [³H]-thymidine (75 µCi) and incubated in medium containing nitrofuran (75 µg/ml). *In vitro*, supercoiled DNA was exposed to the drug in the presence of NADPH, an NADPH generating system, and a 30-60% ammonium sulfate precipitate of *E. coli* B/r extract. In both cases, the amount of supercoiled DNA remaining after incubation was determined by centrifugation in neutral or alkaline gradients. Activated nitrofurazone reacted with covalently closed circular DNA *in vivo* to produce breaks that were detected on neutral sucrose gradients and alkali-labile lesions that were converted to breaks when the damaged DNA was subsequently treated with alkali. DNA treated *in vitro* also contained lesions that were converted to breaks upon treatment with endonuclease preparations obtained from *Micrococcus luteus*. The minicells repaired both breaks and nuclease-susceptible lesions within two hours, but did not repair the alkali-labile lesions within that period. The experiments with the other nitrofurans indicated that there were considerable differences in the degree to which DNA was damaged by activated metabolites of the various derivatives. The potency of these compounds as mutagens and carcinogens was correlated with the amount of damage they caused to minicell DNA. It is likely that the alkali-labile lesions have a molecular basis different from the lesions that result in breaks observed under neutral conditions.

- 4868 MUTAGENICITY OF METRONIDAZOLE: ACTIVATION BY MAMMALIAN LIVER MICROSOMES. (Eng.) Rosenkranz, H. S. (Coll. Physicians and Surgeons, Columbia Univ., New York, N.Y. 10032); Speck, W. T. *Biochem. Biophys. Res. Commun.* 66(2):520-525; 1975.

The widespread usage of metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] to treat human infections was questioned, and the possibility of its mutagenicity in *Salmonella typhimurium* was investi-

gated. Agar plates were inoculated with the indicator strain and test agent (0, 25, 50, 125, 250 µg/plate) in the dark for 46 hr at 37 C. The number of revertants per plate increased from 244 with no metronidazole to 310 revertants with 25 µg/plate; the number of revertants per plate increased to 1,171 by increasing the drug concentration from 25-250 µg. A nitro-reductase-deficient *S. typhimurium* mutant was unable to activate metronidazole to a genetically active mutant. However, incubating of the mutant with metronidazole in the presence of a microsomal preparation from rat liver resulted in a partial restoration of mutagenic activity. When the plates were supplemented with a microsomal preparation and incubated anaerobically, the yield of mutants increased significantly. It has been widely assumed that the activation of metronidazole could be catalyzed solely by enzymes present in protozoans and anaerobic bacteria. The finding that mammalian enzymes can activate metronidazole to a genetically active intermediate may have a direct relevance to the carcinogenicity of this agent.

- 4869 INDUCTION OF THE POLYAMINE-BIOSYNTHETIC ENZYMES IN MOUSE EPIDERMIS BY TUMOR-PROMOTING AGENTS. (Eng.) O'Brien, T. G. (Medical Center, Univ. of Wisconsin, Madison, Wis. 53706); Simsian, R. C.; Boutwell, R. K. *Cancer Res.* 35(7):1662-1670; 1975.

The activities of ornithine and S-adenosyl-L-methionine (S-Ado-Met) decarboxylase were measured in the epidermis of female Charles River mice following treatment with croton oil or 12-*O*-tetradecanoyl-phorbol-13 acetate (TPA). Ornithine assay was accomplished using DL-[2-¹⁴C]ornithine in the incubation mixtures, and 0.5 ml 10% HClO₄ was used to stop the reaction. S-Ado-Met decarboxylase activity was determined by measuring the release of ¹⁴CO₂ from S-adenosyl-L-[carboxyl-¹⁴C]-methionine in the presence of added putrescine as an acceptor of the propylamino moiety derived from decarboxylated S-Ado-Met. A single topical application of 1.0 mg croton oil or 17 nm TPA resulted in a rapid, transient stimulation of ornithine decarboxylase activity. The activity reached a peak (230-fold greater than control) at 4-5 hr after croton oil or TPA treatment and returned to control level by 12 hr. The stimulation of S-adenosyl-L-methionine decarboxylase activity was less pronounced, reaching a peak of activity (6- to 7-fold greater than control) at 9-12 hr after treatment and slowly declining to control level. The stimulation of both enzyme activities was dependent on the dose of TPA applied and correlated well with the promoting ability of these doses on mouse skin. Cycloheximide pretreatment abolished the increase in enzyme activities after TPA application. By measuring the decline of enzyme activity following cycloheximide treatment, enzyme half-lives of 17 and 41 min were obtained for ornithine and S-adenosyl-L-methionine decarboxylase, respectively. 5-Azacytidine pretreatment prevented the stimulation of enzyme activities by TPA, while actinomycin D had no effect. Cordycepin (3'-deoxyadenosine) partially blocked the rise in enzyme activities. It is concluded that within two hours of a single application of active promotor, and before the general increase in total RNA and protein synthesis, the synthesis of specific mRNAs occurs;

this results in greatly increased activities of ornithine and S-Ado-Met decarboxylase.

- 4870 MATCHED-PAIRS STUDY OF RESERPINE USE AND BREAST CANCER. (Eng.) Laska, E. M. (Information Sciences Div., Rockland Res. Inst., Orangeburg, N.Y. 10962); Meisner, M.; Siegel, C.; Fischer, S.; Wanderling, J. *Lancet* 2(7929):296-300; 1975.

A study was undertaken to further investigate the relationship between the use of reserpine and breast cancer. Fifty-five female inpatients at the Rockland Psychiatric center were diagnosed as having breast cancer between 1965 and 1974. These patients were matched with noncancer inpatients with respect to age, year of admission, psychiatric diagnosis, race, and religion. Yearly reserpine use was determined, as were the reasons for its use. Compared with the noncancer patients, the cancer patients showed a greater tendency to be single, childless, obese, and hypertensive; however, this tendency was statistically nonsignificant. Thirty-two cancer patients and 31 controls had received reserpine; in the cancer group, this was primarily for the control of hypertension, while in the noncancer group it was primarily for psychopharmacological purposes. The amount of reserpine received and the number of days on reserpine for each patient were both calculated for each year before the breast cancer diagnosis and for the cumulative number of years since diagnosis. In general, reserpine use was similar in the cancer and control groups, and none of the indicators of relative risk differed significantly from unity. The data indicate that there is no significantly increased risk of breast cancer among women exposed to reserpine for various time-specific definitions of reserpine use.

- 4871 ALTERATION OF METASTASES DISTRIBUTION BY VASODILATING DRUGS. (Eng.) Boeryd, B. (Dept. Pathology, Univ. Goteborg, Sweden); Hagmar, B.; Johnsson, G.; Ryd, W. *Pathol. Eur.* 10(3):197-201; 1975.

The effect of dihydralazine and phenoxybenzamine on the distribution of experimental metastases from intravenously transfused tumor cells, were studied. A methylcholanthrene-induced sarcoma, MCG1-SS, in syngeneic CBA-mice was the source of cells for injection. Mice given 0.02 mg dihydralazine (ip, 30 min before tumor cells) had an average of 10.7 extra pulmonary metastases; compared to 6.1 for controls ($P < 0.001$). Phenoxybenzamine (0.2 mg, ip) increased the number of lung metastases ($P < 0.01$). Both drugs increased the total number of metastases to the liver ($P < 0.05$). These effects of the drugs are probably secondary to their vasodilating effects.

- 4872 INHIBITION OF DIMETHYLHYDRAZINE-INDUCED NEOPLASIA OF THE LARGE INTESTINE BY DISULFIRAM. (Eng.) Wattenberg, L. W. (Univ. Minnesota Med. Sch., Minneapolis). *J. Natl. Cancer Inst.* 54(4):1005-1006; 1975.

The effect of disulfiram, butylated hydroxyanisole

(BHA), and benzyl isothiocyanate in the diet was studied in mice with large bowel neoplasia produced by repeated sc injections of dimethylhydrazine (DMH). Groups of 20 female CF₁ mice were placed on diets of BHA (5 mg/g), disulfiram (5 mg/g), or benzyl isothiocyanate (1.25 mg/g) for 17 wk. The mice were then given 0.7 mg DMH sc weekly for 16 wk. The intestinal tracts were autopsied after 36 wk and the tumors in the tract were counted. All mice in two control groups with no dietary addition, and mice in BHA and benzyl isothiocyanate groups showed multiple tumor formation in the large intestine. Animals fed disulfiram had no lesions. Disulfiram in the diets inhibited tumor formation in the large intestine of mice given DMH.

- 4873 FOLLOW-UP STUDY OF MALE AND FEMALE OFFSPRING OF DES-TREATED MOTHERS: A PRELIMINARY REPORT. (Eng.) Bibbo, M. (The Chicago Lying-in Hosp., Chicago, Ill.); Al-Naqeeb, M.; Baccarini, I.; Gill, W.; Newton, M.; Sleeper, K. M.; Sonek, M.; Wied, G. L. *J. Reprod. Med.* 15(1):29-32; 1975.

A preliminary report of a follow-up study of male and female offspring of mothers who were part of a double-blind placebo-controlled investigation during the years 1951-1952, which was originally aimed at determining the usefulness of diethylstilbestrol (DES) administration in maintaining pregnancy, was made. So far, 84 DES-exposed females, 43 female controls, 42 DES-exposed males and 37 male controls have been examined. Circumferential ridges of the vagina and cervix were seen in 39% of the DES-exposed females but in none of the controls. Colposcopy revealed vaginal epithelial changes in 78% of the DES-exposed females versus 2% in the female controls. Cytology proved to be reliable as a screening test for vaginal epithelial changes in the DES-exposed female. Urine cytology was negative for tumor cells in all patients. The main abnormal finding in the DES-exposed males was that cysts in the epididymis were detected in 10%. No cases of cancer were observed in either the male or female offspring.

- 4874 SPONTANEOUS AND ESTROGEN-PRODUCED TUMORS IN Nb RATS AND THEIR BEHAVIOR AFTER TRANSPLANTATION. (Eng.) Noble, R. L. (Cancer Res. Cent., Univ. British Columbia, Vancouver, Canada); Hochachka, B. C.; King, D. *Cancer Res.* 35(3):766-780; 1975.

The effect of estrogen on transplanted tumors, either of spontaneous origin or the result of prolonged implantation of sc estrogen pellets, was studied in 1.5- to 3-mo-old, male and female, hormone-conditioned and control Nb rats to determine whether hormone conditioning was required for growth. Successfully transplanted tumors were classed as dependent or autonomous only when they showed the same growth patterns for at least three generations and were listed as not growing if they could not be maintained by transplant for three generations. While all spontaneous tumors arising in males and many of those in females were autonomous on transplant, most of the tumors from estrogenized animals continued to require hormones for growth after transplantation;

these included carcinomas of the adrenal cortex, mammary gland, pituitary, pituitary ectopic tissue, ovary (thecoma), uterus (leiomyoma), cervix, vagina (fibrosarcoma), Leydig cells of testis, thymus, pancreas, salivary glands, orbital gland (fibroadenoma), liposarcoma, and lymphoma. All estrogens used, including estradiol, were effective. The incidence of common tumors (adrenal, mammary gland, pituitary) was very low in normal rats, especially in males, but was increased in animals of both sexes after estrogenization, especially in older animals. The incidence of breast tumors after 12 mo was approximately 40% in treated females and 15% in males; the incidence of anterior pituitary tumors were 89-90% after 12 mo. The incidence of mammary tumors was nearly 100% when the pellet was implanted at the age of two weeks and decreased to approximately 15% when the pellet was implanted at age eight weeks.

- 4875 EFFECT OF ESTROGEN-CONTAINING ORAL CONTRACEPTIVES ON URINARY CORTICOSTEROID SULFATE EXCRETION. (Eng.) Fahl, W. E. (Univ. Hospitals Madison, Wis. 53706); Rose, D. P. *Clin. Chim. Acta* 63(2):189-192; 1975.

The excretion of corticosteroid sulfates and free cortisol in urine, and the total plasma cortisol, were determined by competitive protein-binding techniques in 41 women (aged 20-47 yr) receiving an estrogen-containing oral contraceptive and in 53 age-matched controls. Plasma cortisol and urinary corticosteroid sulfate levels were significantly elevated in the oral contraceptive users, and there were no significant differences in the elevations seen in women taking 0.05 mg estrogen and those taking a higher dose. The increases were similar to those observed in pregnancy. The contraceptive steroids did not alter urinary free cortisol levels. The results of this study, together with experimental evidence for estrogen dependence of hepatic sulfurylation, is of interest in light of studies showing the presence of steroid-sulfurylating enzymes in some human breast cancers and elevations of urinary corticosteroids in breast cancer patients.

- 4876 ESTROGEN AND ANTAGONIST-INDUCED STRUCTURAL CHANGES IN THE CERVICO-VAGINAL EPITHELIUM OF IMMATURE RATS. (Eng.) Anderson, W. A. (Dept. Zoology, Howard Univ., Washington, D.C. 20059); Kang, Y. H. *Am. J. Anat.* 144(2):197-207; 1975.

Experimentally induced structural changes in the cervico-vaginal epithelium of 72 virgin female Sprague-Dawley rats (21-23 days old) are described. Groups of six animals were given daily sc injections of one of the following: estradiol-17 β (0.04 μ g/0.1 ml glycerol/24 hr or 1-4 μ g/0.1 ml glycerol/24 hr); estrogen antagonist 1-[[2-(P-[alpha-(P-methoxyphenyl)-beta-nitrostyryl]phenoxy)ethyl]-pyrrolidine (CI-628, 50 μ g/0.1 ml glycerol/24 hr or 500 μ g/0.1 ml glycerol/24 hr); or CI-628 injections followed by estradiol-17 β 30 min later. Control animals were given 0.1 ml glycerol/24 hr. All rats were killed at 12-hr intervals. Estrogen administration resulted in enhanced proliferation of the basal cells, keratin formation in the cervico-

vaginal epithelium and desquamation of the cornified superficial cell layers; CI-628 repressed mitosis and induced mucinogenesis. Combinations of the antagonist and estrogen allowed differentiation of an epithelium composed of both keratin-forming and mucous cells. Estrogen and antagonist both induced synthesis of a cervico-vaginal endogenous peroxidase in the intermediate and superficial layers of the epithelium. Secreted vaginal mucous of antagonist-treated animals stained intensely for exogenous peroxidase. These results emphasize the intrinsic capacity of the cervico-vaginal epithelium to modulate at least two different pathways (i.e., keratogenic and mucinogenic), depending upon the extrinsic hormonal influences.

- 4877 CORRELATION BETWEEN SPECIES LIFE SPAN AND CAPACITY TO ACTIVATE 7,12-DIMETHYLBENZ(a)-ANTHRACENE TO A FORM MUTAGENIC TO A MAMMALIAN CELL. (Eng.) Schwartz, A. G. (Temple Univ. Medical Sch., Philadelphia, Pa. 19140). *Exp. Cell Res.* 94(2):445-447; 1975.

An assay of cell-mediated mutagenesis was used to determine the capacity of cultured X-irradiated fibroblasts from six different mammalian species to convert 7,12-dimethylbenz(a)anthracene (DMBA) to a mutagenic form. The species were rat, guinea pig, rabbit, horse, elephant, and man; these species have potential life spans ranging from 3.5-110 yr. Cultures of V79 cells and the fibroblasts were treated with 0.03% DMBA for 24 hr; the V79 cells were then trypsinized and plated at 3×10^4 and 200 cells/culture dish, for determination of the number of 8-azaguanine (30 μ g/ml) mutants and viability. There was an extremely good inverse correlation between the potential life span of a species and the apparent capacity of its cultured fibroblasts to activate DMBA. The biochemical parameter response for the differential mutation rates remains to be established.

- 4878 SYNTHESIS OF DIEPOXIDES AND DIPHENOL ETHERS OF PYRENE AND DIBENZ[a,h]ANTHRACENE. (Eng.) Agarwal, S. C. (New York Univ. Medical Center, New York, N.Y. 10016); Van Duuren, B. L. *J. Org. Chem.* 40(16):2307-2310; 1975.

The diepoxides, 4,5,9,10-diepoxytetrahydropyrene and 5,6,12,13-diepoxytetrahydrodibenz[a,h]anthracene, were synthesized from the parent hydrocarbons via their respective diozonides and tetraaldehydes. Both epoxides were converted to diphenols. Because of the instability of the diphenols, they were converted to, and characterized as, phenol ethers. The two diphenol ethers derived from diepoxydibenz[a,h]anthracene were characterized as 5,12-dimethoxydibenz[a,h]anthracene and 6,13-dimethoxydibenz[a,h]anthracene. All of these compounds are new, with the exception of 5,12-dimethoxydibenz[a,h]anthracene. These epoxides and their diphenols are important in chemical carcinogenesis studies.

- 4879 RETENTION OF TRITIUM DURING THE BINDING OF TRITIATED BENZO(a)PYRENE TO DNA. (Eng.) Osborne, M. R. (Inst. Cancer Res., Pollards Wood

Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks., HP8 4SP, England); Thompson, M. H.; King, H. W. S.; Brookes, P. *Int. J. Cancer* 16(4):659-664; 1975.

The relative tritium content of benzo(a)pyrene (BP)-deoxyribonucleoside products isolated from DNA having [3 H], [14 C]-BP bound *in vivo* or *in vitro* were determined and compared with that of the starting hydrocarbon and its metabolites. Double-labeled BP was diluted with unlabeled BP and converted to 6-acetoxy-BP and 6-acetoxy-1-nitro-BP. [3 H], [14 C]-BP was added at 8×10^{-5} M to a microsome preparation from the liver of rats, which had previously received an ip injection of 3-methylcholanthrene (40 mg/kg). Chemical conversion of generally tritiated BP to 6 and 1,6-substituted derivatives resulted in 30% and 48% loss of tritium, respectively. Metabolism of [3 H], [14 C]-BP by rat liver microsomes yielded 3-hydroxybenzo(a)pyrene with 30% loss of tritium, a mixture of quinones with 50% loss of tritium and three dihydrodiol metabolites that had retained all the tritium of the parent hydrocarbon. DNA isolated from mouse embryo cells that had been exposed to [3 H], [14 C]-benzo(a)pyrene, and DNA with this hydrocarbon bound following *in vitro* rat liver microsome incubation were degraded enzymically, and the hydrocarbon-deoxyribonucleoside products were isolated. The tritium contents of the products obtained from both DNA samples were very close to those of the original double-labeled benzo(a)pyrene. These results are inconsistent with a phenol or quinone intermediate being responsible for the reaction with DNA, but fully consistent with a diol epoxide intermediate.

- 4880 ARYL HYDROCARBON (BENZO[a]PYRENE) HYDROXYLASES IN LIVER FROM RATS OF DIFFERENT AGE, SEX AND NUTRITIONAL STATUS. DISTINCTION OF TWO TYPES BY 7,8-BENZOFLAVONE. (Eng.) Wiebel, F. J. (Nat'l. Cancer Inst., Bethesda, Md.); Gelboin, H. V. *Biochem. Pharmacol.* 24(16):1511-1515; 1975.

Sensitivity to the synthetic flavonoid 7,8-benzoflavone was used to determine the distribution of the different forms of hepatic aryl hydrocarbon hydroxylase in Sprague-Dawley rats in different biological states. 3-Methylcholanthrene (40 mg/kg) was injected ip in 0.3 ml corn oil/100 g in newborn and adult mice of both sexes. Control animals received corn oil only. After 18 hr animals were killed, and postmitochondrial supernatant and microsomes were prepared from 0.25 M sucrose homogenates. For the aryl hydrocarbon hydroxylase activity assay, each incubation flask contained in a volume of 1.0 ml: 50 μ M Tris-HCl, pH 7.5; 3 μ M $MgCl_2$; 0.5 μ M NADPH; and 0.1 ml postmitochondrial supernatant or 0.1 ml microsomes suspended in sucrose-Tris buffer. 7,8-Benzoflavone was added in 0.01 ml methanol; 100 nM substrate (benzo[a]pyrene) was added in 0.04 ml methanol. The incubation time was ten minutes. The mixture was shaken with 3.0 ml hexane. A 1.0 ml aliquot of the organic layer was extracted with 2 ml of 1 N NaOH, and the fluorescence was measured spectrophotofluorometrically. At least two types of aryl hydrocarbon hydroxylating enzyme systems were identified in rat liver depending on the age, sex,

and nutritional state of the rat as well as their exposure to specific inducers. One type, which was stimulated by the 7,8-benzoflavone, was found in newborn rats and predominated in the liver of adult male rats. This type was inducible by phenobarbital. A second type, which was inhibited by 7,8-benzoflavone, comprised a larger fraction in the liver of adult female rats and was inducible by polycyclic hydrocarbons in immature and mature animals of either sex. The presence of this form in adult female liver was also indicated by the kinetics of the hydroxylase reaction. Removal of solid food for 18 hr not only decreased hepatic aryl hydrocarbon hydroxylase activity in female rats, but also lowered the degree of inhibition by 7,8-benzoflavone. Kinetic data suggest that at low concentrations 7,8-benzoflavone acts as a competitive inhibitor, but at higher concentrations it inhibits the hydroxylation reaction by a more complex mechanism.

- 4881 THE SIGNIFICANCE OF THE *cis*-ACONITIC ACID FOR THE BIOLOGICAL INACTIVATION OF THE 3,4-BENZOPYRENE CANCEROGENESIS. (Ger.) Kallistratos, G. (Forschungsinstitut Borstel, Institut für experimentelle Biologie und Medizin, D-2061 Borstel, Bundesrepublik Deutschland). *Experientia* 31(4):490-491; 1975.

The effect of *cis*-aconitic acid on the carcinogenic effect of 3,4-benzopyrene was studied in young female IMRI mice. A single sc injection of 2.52 mg of 3,4-benzopyrene caused tumor development in 100% of the 30 mice, and death within seven mo. The tumor incidence rate was 77% after the sc injection of the same 3,4-benzopyrene dose together with 10 mg of *cis*-aconitic acid. The tumor incidence was lowered to 63% by the addition of ethanol (which increased the solubility of *cis*-aconitic acid). The tumor incidence was 18% in mice injected with 2.52 mg of benzopyrene together with 30 mg of *cis*-aconitic acid with additional ethanol. Since *cis*-aconitic acid is a metabolite occurring within the citric acid cycle, it may be theoretically significant for the biological inactivation of the carcinogenic action of 3,4-benzopyrene.

- 4882 EFFECT OF BENZO(A)PYRENE INDUCTION OF LIVER AND LUNG METABOLISM IN ADJUVANT-DISEASED RATS. (Eng.) Carlson, R. P. (Jefferson Medical Coll., Philadelphia, Pa.); Ciaccio, E. I. *Biochem. Pharmacol.* 24(20):1893-1895; 1975.

Aryl hydrocarbon hydroxylase levels were measured in rats injected with *Mycobacterium butyricum* to investigate the effects of benzo(a)pyrene treatment on the microsomal drug-metabolizing system in the lung and liver of these adjuvant-diseased animals. Benzo(a)pyrene (4 mg/ml in 5% Tween 90) was injected ip at 25 mg/kg in male Sprague-Dawley rats two days before adjuvant treatment. *M. butyricum* (5 mg/ml) in light mineral oil at 0.1 ml was administered sc on day 0. Controls received only mineral oil. On days 0, 9, and 14, paw circumferences were measured at the lateral malleolus. The livers and lungs were removed from the various groups on days 0, 7, and 14, and were assayed for

aryl hydrocarbon hydroxylase activity. The substrate, 50 µg benzo(a)pyrene in 0.1 ml acetone, was added to a reaction flask containing 0.5 ml of 1% liver supernatant or 0.5 ml of 10% lung supernatant, and the reaction was allowed to continue for 12 min for liver and ten minutes for lung. Benzo(a)pyrene metabolites were extracted into ligroine and measured by spectrophotofluorometry. Paw edema was not evident until after the ninth day, and was not affected by benzo(a)pyrene. Liver aryl hydrocarbon hydroxylase activity was elevated 4-fold within two days by benzo(a)pyrene treatment. Nine days after benzo(a)pyrene administration, the liver aryl hydrocarbon hydroxylase lost its induced activity. Aryl hydrocarbon hydroxylase activity in adjuvant-benzo(a)pyrene-treated rats was only slightly higher than that of adjuvant controls at the seventh day, but the difference was statistically significant. Benzo(a)pyrene treatment raised the lung aryl hydrocarbon hydroxylase levels approximately 9-fold; this activity remained elevated much longer in lung than in liver. After 14 days, the activity was still 5- to 6-fold higher than in the normal controls. Benzo(a)pyrene injections also appeared to protect against impairment of the lung microsomal drug-metabolizing system for 14 days. These results suggest that benzo(a)pyrene does not act as an inducer for detoxification mechanisms of adjuvant, even though it does prevent the deterioration of specific extrahepatic microsomal drug-metabolizing system enzymes.

- 4883 CYTOCHROME P-450-LINKED ACTIVATION OF 3-HYDROXYBENZO(α)PYRENE. Capdevila, J. (Dept. Forensic Medicine, Karolinska Inst., S-104 01 Stockholm 60, Sweden); Jernstrom, B.; Vadi, H.; Orrenius, S. *Biochem. Biophys. Res. Commun.* 65(3): 894-900; 1975.

The formation and reactivity of a new metabolite that binds DNA was studied. Incubation of 3-hydroxybenzo(α)pyrene with rat lung microsomes in the presence of NADPH and oxygen resulted in the formation of a metabolite bound covalently to DNA. The reaction was inhibited by carbon monoxide and α-naphthoflavone and was increased more than 10% by pretreatment of the rats with 3-methylcholanthrene. The authors propose that the reaction involves the formation of an epoxide due to the presence of the 3-hydroxy group.

- 4884 UPTAKE, METABOLISM, AND PERSISTENCE OF 3-METHYLCHOLANTHRENE IN RAT EMBRYO CELLS INFECTED WITH MURINE LEUKEMIA VIRUS. (Eng.) Zimmerman, E. M. (Microbiol. Assoc., Bethesda, Md.); Kouri, R. E.; Higuchi, K.; Laird, F.; Freeman, A. E. *Cancer Res.* 35(1):139-143; 1975.

The cellular uptake, metabolism, and persistence of 3-methylcholanthrene (MCA) was studied in Fischer (F344/f Mai) rat embryo cultures of both high passage and low passage cells, infected with Rauscher leukemia virus (F1706V and F2304V). Controls (F1706C and F2304C) were not infected. Cells were re-fed a medium containing 0.4 µM [6-¹⁴C] MCA, which produced no visible cytotoxicity, when examined over a 48 hr per-

od. Replicate cultures confirmed transformability in the low passage F2304V. F2304C showed no transformation within 20 passages. The uptake of labeled MCA was determined using a cellular NaOH digest with aquasol in an LS-250 liquid scintillation counter. Persistence of MCA was determined by the same method using cells re-fed an MCA-free medium for 48 hr. The total protein per culture was determined. The binding of MCA to macromolecules was determined by extracting DNA, RNA, and protein and isolating each fraction. Labelled MCA in each fraction was again determined using Aquasol and the scintillation counter. Metabolism of MCA was measured using the ability of the cell to convert benzo-pyrene (BP) from an organic soluble to an aqueous acetone-soluble form. None of the indices were significantly different in the F1706V or F2304V groups as compared to the controls. The indices were similarly unaffected by cell passage level. The results suggest that the virus itself may play a direct role in transformation perhaps by offering oncogenic information that can be derepressed due to the effects of the chemical on the cell, rather than indirectly affecting permeability or metabolism of the chemical.

385 **GANGLIOSIDES OF CHEMICALLY AND VIRALLY TRANSFORMED RAT EMBRYO CELLS.** (Eng.) Langenbach, R. (Univ. Nebraska Med. Cent., Omaha). *Biochim. Biophys. Acta* 388(2):231-242; 1975.

Differences in gangliosides of rat embryo cells transformed by 3-methylcholanthrene and Rauscher leukemia virus (alone or combined) and normal cells were investigated. Saturation densities were determined three days after seeding, and plating efficiencies were determined 5-8 days after seeding. After plating 10^4 cells, cell growth was determined at 24 hr intervals for four days. Labeled gangliosides were isolated by thin-layer chromatography and subjected to mild or vigorous acid hydrolysis to liberate sialic acid, hexose, and hexosamines. The plating efficiency of the transformed lines was 91-94%, compared to 54% for controls. Doubling times for transformed lines were decreased to half those of controls with the 3-methylcholanthrene treatment. Saturation density (cells/dish $\times 10^{-6}$) for the control, Rauscher leukemia, 3-methylcholanthrene and combined transformants were 6.8, 15.0, 22.5 and 12.0 respectively. Examination with the electron microscope revealed elongated cells with rough surfaces for the leukemia transformants and the leukemia-methylcholanthrene-treated cells. The 3-methylcholanthrene-treated cells showed a great propensity for budding up. The [14 C]glucosamine uptake was increased in all transformed cells. The presence of six gangliosides was investigated with all transformed cells showing a predominance of the GM₃ ganglioside. The GM₂ ganglioside predominated in the control cells. The chromatographic mobility of ganglioside GD_{1b} decreased and ganglioside GT increased in transformed cells. The majority of the radioactive distribution of transformed gangliosides was with galactosamine and sialic acid moieties. The ratio of radioactivity AcNeu to glycolNeu was 1.8 for controls and 5.3-7 for transformed gangliosides. These results indicate that the ganglioside patterns of all cell lines are complex, and that differences between the normal

and transformed lines are quantitative rather than qualitative.

4886 **ZINC INTAKE, NEOPLASTIC DNA SYNTHESIS, AND CHEMICAL CARCINOGENESIS IN RATS AND MICE.** (Eng.) Duncan, J. R. (Dep. Biochem., Univ. Natal, Pietermaritzburg, South Africa); Dreosti, I. E. *J. Natl. Cancer Inst.* 55(1):195-196; 1975.

The effect of different levels of zinc on DNA synthesis in grafted rat tumors and the relationship between zinc status and 3-methylcholanthrene-induced carcinogenesis in mice were examined. Female Wistar rats receiving 150-mg im implants of a hepatoma induced by 3'-methyl-4-dimethylaminoazobenzene into one hind leg. An experimental diet consisting of EDTA acid-extracted soybean meal, sucrose, salts, vitamins, and various levels of zinc (0.4-2,500 µg/g ration) was given for three weeks. Control animals received the same diet supplemented with 60 µg zinc/g ration. After three weeks, 50 µCi [3 H]thymidine was injected ip and two hours later, the concentration and specific activity of DNA were determined in excised tumors. In another study, female Swiss mice were fed the same experimental rations for ten weeks, during which time they were painted twice weekly on the shaved interscapular region with 0.5% methylcholanthrene. DNA synthesis in the tumors was significantly reduced in rats maintained on diets low (0.4 µg/g) or high (≥ 500 µg/g) in zinc when compared with the control animals. In the experiment concerning methylcholanthrene-induced carcinogenesis, both papilloma development and the incidence of the malignancy were significantly reduced in mice consuming the zinc-deficient and supplemented diets. It is suggested that the finding that DNA synthesis is considerably lowered in tumors transplanted into rats given high or low levels of zinc supports a previous suggestion that decreased tumor growth under these conditions arises from a block in the cell division cycle at the level of DNA replication. The considerable reduction in carcinogenesis obtained at levels of 500 µg/g ration in the methylcholanthrene experiment suggests that dietary zinc offers some measure of control of chemical carcinogenesis because toxicity of the trace element in rats occurs only at levels above 2,500 µg/g ration.

4887 **INTERACTIONS BETWEEN SOLUBILIZED CYTOCHROME P-450 AND HEPATIC MICROSOMES.** (Eng.) Yang, C. S. (New Jersey Medical Sch., Newark, N.J. 07103); Strickhart, F. S. *J. Biol. Chem.* 250(20):7968-7972; 1975.

The interactions between solubilized cytochrome P-450 (cytochrome P-448) and rat liver microsomes were studied using microsomes from untreated male Sprague-Dawley rats and cytochrome P-450 purified from the livers of 3-methylcholanthrene-pretreated male Long-Evans rats. The microsomes were incubated with solubilized cytochrome P-448 at 37 C for 30 min, after which the benzpyrene-hydroxylase activity of the microsomes was assayed; the NADPH-dependent reduction of cytochrome P-450 was measured; and determinations were made of the extent of binding of cytochrome P-448 to the microsomes and

the effect of NADH on the cytochrome P-448-enriched system. The solubilized enzyme preparation produced a concentration-dependent increase in microsomal benzpyrene-hydroxylase activity; there was maximum increase to about five times the original activity being observed with 4.7 nM of exogenous cytochrome P-448. The increase in catalytic activity appeared to be proportional to the bound cytochrome P-448, and it appeared likely that the exogenous hemoprotein was a functional part of the microsomal monooxygenase system. The enzyme preparation did not catalyze the monooxygenase reactions unless NADPH-cytochrome P-450 and phospholipids were also present. The microsome-bound exogenous cytochrome P-450 could be enzymically reduced by NADPH, but only when it was incorporated into the microsomal membrane. The NADPH-reducible cytochrome P-450 molecules were not randomly distributed in the membrane, and the rate of their lateral mobility was not high. The addition of solubilized cytochrome P-450 enhanced both NADH-supported microsomal benzpyrene-hydroxylation and the NADH synergism of the NADPH-supported reaction. It is proposed that the added cytochrome P-450 became incorporated into the microsomal membrane and became a functional part of the microsomal monooxygenase system.

- 4888 STUDIES ON SOURCES OF ENVIRONMENTAL ALKYLATING AGENTS. (Eng.) Norpoth, K. (Institut für Staublungenforschung und Arbeitsmedizin der Universität Münster, 44 Münster (West Germany). *Mutat. Res.* 29(2):294; 1975.

Alkylating compounds can be determined in the nanogram range using the chromogen 4-pyridinecarboxaldehyde-2-benzothiazolylhydrazone. Reactive compounds were fed in auto exhaust fumes, mold cultures, tobacco smoke, and fumes resulting from limited-aeration smouldering of plastics and paper. These products react with 4-(4-nitrobenzyl)pyridine so they may be considered alkylating agents.

- 4889 INCREASED URINARY EXCRETION OF NUCLEIC ACID AND NICOTINAMIDE DERIVATIVES BY RATS AFTER TREATMENT WITH ALKYLATING AGENTS. (Eng.) Chu, B. C. F. (Royal Cancer Hosp., London SW3 6JB, Great Britain); Lawley, P. D. *Chem. Biol. Interact.* 10(5):333-338; 1975.

The effect of alkylating agents on the urinary excretion of deoxycytidine and thymidine was examined in female CB rats. Rats given ip injections of di-(2-chloroethyl)methylamine (5 mg/kg), *N*-methyl-*N*-nitrosourea (50 mg/kg) and *N*-ethyl-*N*-nitrosourea (50 mg/kg) excreted significantly larger amounts of deoxycytidine and thymidine 0-24 hr after treatment. Ethyl methanesulfonate (200-400 mg/kg) and dimethylnitrosamine, DMN, (30 mg/kg) gave negative results in this respect, but all five alkylating agents increased the excretion of 1-methyl-nicotinamide. In addition, a larger quantity of 7-methylguanine and uric acid was excreted after DMN treatment. 1,4-Dimethanesulfonylbutane, 2,2-dichlorovinyl dimethyl phosphate, 5-fluorouracil, cytosine arabinoside, 2-acetylaminofluorene, and 7-bromomethylbenz[a]anthracene gave negative results

at concentrations of 50, 10, 60, 60, 20, and 30 mg/kg, respectively. It has been previously suggested that alkylating agents exert their effects by inactivating DNA as a template for DNA replication. The positive results in this study may thus indicate those compounds which are more efficient in reacting with DNA, or those which induce similar specific DNA damage. Those compounds giving negative results may be more easily hydrolyzed and inactivated before they reach the DNA, or be too unevenly distributed in the animal to allow widespread damage to DNA.

- 4890 HETEROGENEOUS DISTRIBUTION OF DNA ALKYLATION PRODUCTS IN RAT LIVER CHROMATIN AFTER *IN VIVO* ADMINISTRATION OF *N,N*-DI[¹⁴C]METHYLNITROSAMINE. (Eng.) Cooper, H. K. (Max-Planck-Institut für Hirnforschung, 5 Köln 91 (Merheim), Ostmerheimerstrasse 200 West Germany); Margison, G. P.; O'Connor, P. J.; Itzhaki, R. F. *Chem. Biol. Interact.* 11(6):483-492; 1975.

The degradation of poly-L-lysine (PL)-bound DNA chromatin by DNase-I was used to elucidate the heterogeneous distribution of alkylated products in the DNA. Wistar rats were injected ip with *N,N*-di[¹⁴C]methylnitrosamine ([¹⁴C]DMN, 3.34 mCi/mM), the alkylating agent. PL is known to bind to approximately 50% of chromatin DNA rendering it undegradable by DNase I. The experiments indicated that by using a chromatin-PL complex, 41% is degraded and 59% is resistant with about equal specific activity. Chromatin alone afforded 94% degradation and 6% resistance with a particularly high specific activity in the resistant portion. Using column chromatography, RNA was found to comprise a substantial portion of the resistant section of the untreated chromatin. All the RNA of the treated chromatin was found in the resistant portion. Knowing the levels of alkylation and the DNA and RNA fractions of the resistant chromatin (\pm PL), a simple proportionality equation was applied to the results. This clearly showed a heterogeneous distribution of alkylated products in DNA. The alkylation in DNA was lower in the PL-bound regions. This heterogeneous distribution may result as an initial difference in the reaction of DNA or to differences in the rate of repair.

- 4891 *N*, α -ACETOXYETHYL-*N*-ETHYL-NITROSAMINE: A PRECURSOR OF THE BIOLOGICALLY EFFECTIVE METABOLITE OF *N,N*-DIETHYLNITROSAMINE. (Eng.) Fahmy, O. G. (Royal Cancer Hosp., Fulham Road, London SW3 6JB England); Fahmy, M. J.; Wiessler, M. *Biochem. Pharmacol.* 24(21):2009-2012; 1975.

The comparative genetic properties of diethylnitrosamine (DEN) and its α -acetoxy derivative, *N*, α -acetoxyethyl-*N*-ethyl-nitrosamine (AcODEN) were studied in *Drosophila melanogaster* (Oregon-K strain). The two compounds were found to have equivalent cytotoxicity at a molarity ratio of 10 for DEN/AcODEN, and this ratio was therefore employed. DEN (20 mM) and AcODEN (2 mM) were dissolved in dimethylformamide/Arachis oil (2%

vol/vol) and given by micro-injection into the hemocoel of adult XY-bb male *Drosophila*. Cytotoxicity and mutagenicity were measured for all stages of spermatogenesis. Genetic effects were assayed by recording the response of whole X-chromosomes as well as RNA-forming genes. AcODEN induced a significantly higher mutation frequency on RNA genes, the response of which has been shown to be a sensitive indicator of carcinogenic potential. The yield of ribosomal DNA mutations for DEN and AcODEN was about the same, but for the overall X-chromosome recessives the effect of AcODEN was doubled. The mutagenic activities of DEN and AcODEN on the various stages of spermatogenesis were qualitatively similar; however, quantitatively, the ratio of the mean mutation frequencies for the whole testicular tissue was 1.7 ± 0.2 for AcODEN/DEN. It is concluded that AcODEN is the proximate mutagen of DEN.

4892 MUTAGENICITY OF α -ACETOXY-DIALKYLNITROSAMINES: MODEL COMPOUNDS FOR AN ULTIMATE CARCINOGEN. (Eng.) Okada, M. (Tokyo Biochemical Res. Inst., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan); Suzuki, E.; Anjo, T.; Mochizuki, M. *Gann* 66(4):457-458; 1975.

The mutagenicity of α -acetoxy-dialkylnitrosamines for microorganisms was demonstrated without using any metabolic activation system. The compounds tested were N-butyl-N-(1-acetoxybutyl)-nitrosamine (I), N-butyl-N-(acetoxy-methyl)-nitrosamine (IIa), N-sec-butyl-N-(acetoxymethyl)nitrosamine (IIa), and N-tert-butyl-N-(acetoxymethyl)nitrosamine (IVa). Compounds Ia, IIa, and IIIa had a positive effect in a *rec*-assay method using Marburg strains of *Bacillus subtilis* 17A (*rec*+) or 45T (*rec*-). *Salmonella typhimurium* strain TA1535 was used for quantitative testing of mutagenicity. The results demonstrated a good linear relationship between the number of revertant colonies and the concentration of the test compounds. The structure of the butyl chains in the N-butyl-N-(acetoxymethyl)nitrosamines profoundly affected the activity in the order of butyl (IIa) > sec-butyl (IIa) > tert-butyl (IVa), the last being inactive. These results support the α -hydroxylation hypothesis that metabolic activation of dialkylnitrosamines leads to an ultimate alkylating species, probably a carbonium ion.

4893 PHOSPHOTRIESTERS IN RAT LIVER DEOXYRIBONUCLEIC ACID AFTER THE ADMINISTRATION OF THE CARCINOGEN *NN*-DIMETHYLNITROSAMINE *IN VIVO*. (Eng.) O'Connor, P. J. (Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, U. K.); Margison, G. P.; Craig, A. W. *Biochem. J.* 145(3):475-482; 1975.

The formation of phosphotriesters in the liver DNA of male Wistar rats treated *in vivo* with N,N-di(14 C)-methylnitrosamine (2 mg/kg, ip, given 3 hr before sacrifice) was studied. Samples of DNA were isolated from the rat livers and analyzed by chromatography on Dowex 50. Samples from the column effluents were counted for radioactivity. Alkyl

phosphate residues formed in the DNA after treatment with N,N-dimethylnitrosamine accounted for 10% of the total products obtained after phenol isolation. In addition, an unidentified fraction of up to 10% of the radioactivity was released from the DNA together with the 3- and 7-methyl-substituted purines when the DNA was heated in neutral solution. This material was not detected after HClO₄ precipitation and freeze-drying of the alkyl purine fraction, and no uncharged materials were detected when the early eluted products from Dowex 50 chromatography were freeze-dried and re-chromatographed on DEAE-cellulose. Based on these results, a blocking of diesterase action *in vivo* would be expected to arise from the chemical modification of DNA after treatment with N,N-dimethylnitrosamine. The distal position of the methyl groups bound to the phosphate residues would be expected to neutralize the net negative charges on the DNA phosphate groups and to hinder the binding of chromatin proteins to the phosphodiester backbone. On the other hand, base modifications which affect the base-pairing regions of the DNA molecule might be expected to be of greater significance for the mutational aspects of the action of these carcinogenic agents when base substitutions are envisaged.

4894 STUDIES ON LIVER CHROMATIN FROM RATS TREATED WITH DIMETHYLNITROSAMINE.

(Eng.) Cooper, H. K. (Max-Planck-Institute fur Hirnforschung, 5 Koln Merheim, Osterheimer Strasse 200, West Germany); Itzhaki, R. F. *Biochim. Biophys. Acta* 407(3):263-272; 1975.

The effect of C-labeled dimethylnitrosamine (2 or 30 mg/kg, ip) and methyl methanesulfonate (50 mg/kg, ip) on the methylation of hepatic chromatin-associated DNA, RNA, histone, and nonhistone proteins and on the composition and physical confirmation of the liver chromatin were studied in male Wistar rats. The animals were killed five hours after dimethylnitrosamine treatment and two hours after methyl methanesulfonate treatment. The liver chromatin was prepared, and the histones and nonhistone proteins were subjected to electrophoresis on polyacrylamide gels. The radioactivity in the chromatin DNA and RNA was counted, and the labeled chromatin DNA was subjected to base analysis. The electric birefringence of the chromatin was also determined. Preparations of normal rat liver chromatin averaged 32% DNA, 3% RNA, 43% histone, and 22% nonhistone protein. Drug treatment changed neither this composition nor the electrophoretic profiles of the histones and nonhistone proteins. Five hours after [14 C]dimethylnitrosamine treatment (2 mg/kg), the mean labeling values of the DNA, RNA, and histones were 330 dpm/mg, 18,000 dpm/mg, and 460 dpm/mg, respectively; the value for the original chromatin was 4,230 dpm/mg. DNA alkylation was fairly uniform throughout the liver. In contrast to the DNA, most of the RNA radioactivity was metabolically incorporated into adenine and guanine. The amount of label in the DNA and RNA greatly exceeded that in the histones, and the nonhistone proteins were labeled even less. The results of the electric birefringence studies suggest that methylation may result in both

interparticle cross-linking and some localized loosening of the DNA-protein complex.

4895 TUMOR INDUCTION IN RATS BY FEEDING HEPTAMETHYLENIMINE AND NITRITE IN WATER. (Eng.)

Taylor, H. W. (Biol. Div., Oak Ridge Natl. Lab., Tenn.); Lijinsky, W. *Cancer Res.* 35(3):812-815; 1975.

Tumor development was studied in male and female Sprague-Dawley rats whose diet included either 0.2% heptamethyleneimine hydrochloride, alone or in combination with 0.2% sodium nitrite (5 days/week for 28 weeks), or 0.2% sodium nitrite for 104 weeks. Animals receiving either salt alone survived for up to two yr, and only tumors encountered in control animals were observed to have developed, usually of endocrine origin. In the animals receiving the combined treatment, most males were dead at 80 weeks and most females were dead at 50 weeks, and 27 of 30 animals had tumors not seen in the control groups; 16 had squamous carcinoma of the lung, 25 had tumors of the oropharynx, tongue, esophagus, and forestomach, and a few had tumors in the nasal cavity and trachea. Formation of a nitrosamine is the presumed cause of tumor induction, and the use of this system as a model for human lung cancer is discussed.

4896 GENETIC STUDIES ON HUMAN LYMPHOBLASTOID CELL LINES: ISOZYME AND CYTOGENETIC HETEROGENEITY IN A CELL LINE, WITH EVIDENCE FOR LOCALIZATION OF THE *PEP A* LOCUS IN MAN. (Eng.)

Arthur, E. (Western General Hosp, Edinburgh, Scotland); Steel, C. M.; Evans, H. J.; Povey, S.; Watson, B.; Harris, H. *Ann. Hum. Genet.* 39(1):33-42; 1975.

One hundred and thirty-three clones (60 mutagen-treated, 73 controls) of the human male lymphoblastoid cell line F 137 were examined for the electrophoretic pattern of over 30 enzymes. *N*-methyl-*N'*-nitrosoguanidine was added to F 137 medium at a final concentration of 1 or 2 µg/ml and remained in contact with mutagen for 30 or 60 min at 37 C. Karyotyping was performed by adding 0.05 µg dimethyl colchicine to a 5-ml cell suspension. The cells were harvested 30-90 min later and examined by UV microscopy. The clones were examined by starch-gel electrophoresis for enzymes determined by 34 autosomal and four X-linked loci. In nine instances, there was loss of activity of one allele of an X-linked or heterozygous autosomal locus. Seven of these involved the *Pep A* locus, and in every case the change was from the *Pep A* 2-1 phenotype to *Pep A* 2. Cytogenetic analysis of the parent line revealed a number of variants on the modal karyotype. On cloning, there appeared to be some selection for survival of nonmodal cells: The proportions of the cytogenetically distinct populations within the bulk culture varied over a period of many months. There was a strong correlation in individual clones between loss of activity of the product of the *Pep A*¹ allele and the presence in the cells of a 9/18 translocation. In addition, there was one clone of phenotype *Pep A* 2 with a deletion of part of the long arm of chromosome 18. The data confirms the assignment of the *Pep A* structural locus to the

distal half of the long arm of chromosome 18 and localizes it with some precision to the qter region. The *Pep A* 2 phenotype of the clones containing the 9/18 translocation could be the result of a small deletion eliminating the *Pep A*¹ allele but not large enough to be detected cytogenetically. Alternatively, inactivation of the *Pep A*¹ allele may have occurred as a position effect resulting from the close association of heterochromatin from the centromere of 9 with the qter region of 18.

4897 PHOTOCHEMICAL FORMATION OF NITROXIDE RADICALS FROM CARCINOGENIC *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE AND RELATED COMPOUNDS. (Eng.)

Toki, Y. (Natl. Cancer Center Res. Inst., Chuo-ku, Tokyo 104, Japan); Imamura, A.; Nagata, C.; Nakadate, M. *Photochem. Photobiol.* 21(6):387-391; 1975.

N-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and related *N*-alkyl-*N*-nitroso compounds, (e.g., *N*-ethyl, *N*-propyl, and *N*-butyl-*N'*-nitro-*N*-nitrosoguanidine) were analyzed photochemically to identify the free radicals produced in organic solvents. An oxygen-saturated 5.0 x 10⁻⁵ M solution of the ¹⁵N-labeled compound in solvent (benzene, tetrahydrofuran and methanol) was placed in a quartz tube and illuminated with a medium pressure (35 cm) mercury arc lamp at a distance of 10 cm. Gas dissolved in the sample was then removed by several freeze-pump-thaw cycles. The structure of the resultant free radical was studied by the electron paramagnetic resonance method (EPR), measurement of the electronic absorption spectra, and molecular-orbital calculations. The EPR signal of MNNG indicated that the protons of the methyl group adjacent to the nitrogen interacted with the unpaired electron because when the methyl group was replaced by ethyl, propyl, or butyl the EPR signal changed from six peaks to five peaks. The EPR spectrum of photochemically treated *N*-methyl-*N'*-nitro-*N*-nitroso-(¹⁵NO)guanidine was the same as that of the MNNG (six peaks) indicating that the nitroso group of MNNG was not included in the free radical formed. In fact, the nitroso group was removed by the illumination of the benzene solution of the compounds. Oxygen is essential for formation of the free radical since degassed solutions of the compounds gave no signal. Absorption spectra studies of the gassed and anoxic solutions demonstrated fission of the nitroso group occurred without participation of oxygen. Molecular orbital calculations were used to complete the identification of the free radical as the amino form of the nitroxide radical. Illumination of *N*-alkyl-*N'*-nitro-*N*-nitrosoguanidines in organic solvents causes release of the nitroso group and oxygen attack at the *N*-alkyl nitrogen, and the free radical formed is the amino form of the nitroxide radical.

4898 ISOLATION OF HEAT- AND COLD-SENSITIVE MUTANTS OF CHINESE HAMSTER LUNG CELLS AFFECTED IN THEIR ABILITY TO EXPRESS THE TRANSFORMED STATE. (Eng.)

Miyashita, K. (Res. Inst. for Microbial Diseases, Osaka Univ., Suita, Osaka 565, Japan); Kakunaga, T. *Cell* 5(2):131-138; 1975.

A clone of spontaneously transformed Chinese hamster lung cells (actively growing) was exposed to N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) (0.2 µg/ml for eight hr at 34.5 C), and six heat-sensitive and three cold-sensitive mutants were isolated after selection for inability to form colonies in soft agar at 39.5 C and 34.5 C, respectively. The heat-sensitive mutants had growth characteristics of transformed cells at 34.5 C, but exhibited a normal phenotype at 39.5 C. By contrast, cold-sensitive mutants displayed the characteristics of the normal cells at 34.5 C and converted to a transformed phenotype at 39.5 C. Temperature shift experiments showed that the colony-forming ability of both types of mutants was fully reversible. All of the mutants were able to grow well at both permissive and non-permissive temperatures when grown on the surface of plastic dishes. The mutants provide many advantages for comparative studies of the transformed phenotype, including a high plating efficiency, relative genetic homogeneity, and stable temperature-dependent properties.

4899 CHROMOSOMAL PROTEINS OF RAT BRAIN: INCREASED SYNTHESIS AND AFFINITY FOR DNA FOLLOWING A PULSE OF THE CARCINOGEN ETHYLNITROSO-UREA *IN VIVO*. (Eng.) Augenlicht, L. H. (Abteilung Physikalische Biologie, Max Planck-Institut für Virusforschung, 74 Tübingen, West Germany); Biessmann, H.; Rajewsky*, M. F. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):431-438; 1975.

A single pulse of ethylnitrosourea (EtNU, 75 µg/g, im), administered to 10-day-old BD IX-rats, specifically resulted in a high incidence of neuroectodermal tumors in the CNS and the peripheral nervous system. At five days after an EtNU-pulse, analyses of protein-DNA interactions were performed using chromatin dissociation and reassociation experiments, following incorporation of radioactive leucine into brain chromosomal proteins (CP) during short-term suspension culture. In comparison with 15-day-old control animals, the brain cells of EtNU-treated rats exhibited (i) an increased rate of CP synthesis, and (ii) an increased affinity of the newly synthesized CP for brain DNA of both control and EtNU-treated animals. This is believed to be the first reported instance in which the binding of CP to DNA in a high-risk tissue has changed in the early phase of the carcinogenesis process.

4900 CHRONIC INHALATION OF NICKEL OXIDE AND CIGARETTE SMOKE BY HAMSTERS. (Eng.) Wehner, A. P. (Biology Dept., Battelle, Pacific Northwest Lab., Richland, Wash. 99352); Busch, R. H.; Olson, R. J.; Craig, D. K. *Am. Ind. Hyg. Assoc. J.* 36(11):801-810; 1975.

The potentiating effect of cigarette smoke on the harmful effects of NiO was studied in 102 2-mo-old male Syrian hamsters. The animals received lifespan exposures to a respirable aerosol of NiO, seven hours per day, five days per week. Half of the animals were also exposed to cigarette smoke in a modified Hamburg II smoking machine, twice before

and once after the daily dust exposure. At each smoke exposure, the animals received a continuous nose-only exposure of about ten minutes duration. Controls received sham-dust and sham-smoke exposures or sham-dust and actual smoke exposures. In animals exposed to NiO, NiO particulate accumulation on the alveolar septa was the first change; the particulate material appeared to be located both intra- and extracellularly. Emphysema appeared in animals that died early in the experiment. Animals dying, later showed an increased proliferative and inflammatory cellular response with increasing lung consolidation. Hyperplasia of the bronchial and bronchiolar epithelium tended to increase as lung consolidation became more severe. Histopathologically, there was no marked difference between the NiO- plus smoke-treated group and the NiO- plus sham-smoke-treated group, except for the presence of "smoke cells" and a significant increase in laryngeal lesions in the smoke-exposed hamsters. With the exception of pneumoconiosis, there was no significant difference in the incidence of respiratory tract lesions between the NiO- plus sham-smoke-treated group and sham controls, or between the NiO- plus smoke-treated group and smoke-treated controls. The occurrence of musculoskeletal tumors was confined to NiO-exposed hamsters. The smoke-exposed groups lived significantly longer ($p < 0.01$) than their sham-smoke cohorts, and chronic cigarette smoke inhalation significantly ($P < 0.01$) depressed the mean body weights of the exposed groups compared with their sham-exposed cohorts. Thus, inhaled NiO was neither carcinogenic nor particularly toxic in hamsters and chronic cigarette exposure in combination with NiO or sham dust exposures resulted in significantly lower body weights and increased survival time.

4901 CHEMICAL STUDIES ON TOBACCO SMOKE. XXXIII. N'-NITROSONORNICOTINE IN TOBACCO: ANALYSIS OF POSSIBLE CONTRIBUTING FACTORS AND BIOLOGIC IMPLICATIONS. (Eng.) Hecht, S. S. (Naylor Dana Inst. Disease Prevention, Valhalla, N. Y. 10595); Orna, R. M.; Hoffmann, D. *J. Natl. Cancer Inst.* 54(5):1237-1244; 1975.

Preparative thin-layer chromatography followed by gas chromatography and mass spectroscopy were used to determine the presence of nitrosornicotine (NNN) and N'-nitrosoanabasine (NAB) extracted chemically from different tobaccos. For quantitative determinations, NNN-2'-¹⁴C (4 x 10⁵ dpm, 2.5 µg/50-60 g tobacco) was used as an internal standard. NNN was found in the unburned tobacco of commercial products at concentrations between 0.3 and 88.6 µg/g. The highest levels were observed in highly fermented snuff (29.1 µg/g) and fine cut chewing tobacco (88.6 µg/g). NAB was not detected (<0.5 ng/g) in any tobacco examined, but two new components, N'-carbomethoxynornicotine and N'-carbomethoxyanabasine, were found and analyzed. An attempt was made to correlate NNN concentrations in tobacco to other parameters such as tobacco pH, the curing process used, or concentrations of nitrite, nitrate, and alkaloids in tobacco. The curing process might be important in NNN formation, allowing a bacterial or enzymatic nitrosation of nicotine. NNN amounts were obtained for fine cut chewing tobacco incubated

with saliva. An increase of 44% (127 μ g NNN/g) over the amount found in the original chewing tobacco was observed. The biological implications of this finding are discussed.

- 4902 MUTATION INDUCTION IN CHINESE HAMSTER V79 CELLS BY TWO VINYL CHLORIDE METABOLITES, CHLOROETHYLENE OXIDE AND 2-CHLOROACETALDEHYDE. (Eng.) Huberman, E. (Dept. Genetics, Weizmann Inst. Science, Rehovoth, Israel); Bartsch, H.; Sachs, L. *Int. J. Cancer* 16(4):639-644; 1975.

The mutagenic effect of chloroethylene oxide and 2-chloroacetaldehyde on Chinese hamster V79 cells is reported. Cells were seeded 200/dish and incubated. Ouabain-resistant and 8-azaguanine-resistant cells were cultured from a portion of the control. These served as genetic markers to indicate mutation frequency. Cloning efficiency and mutation frequency were plotted against increasing concentrations of the test metabolites. The control cells grown on dimethylsulfoxide (DMSO) exhibited a cloning efficiency of 93%. The number of 8-azaguanine-resistant mutants per 10^5 survivors grown in DMSO was eight, while there were three ouabain-resistant mutants per 10^6 survivors. With increasing concentrations of chloroethylene oxide (3-25 μ M), the cloning efficiency of the treated cells decreased from 89% to 3.3%, while the number of 8-azaguanine-resistant mutants per 10^5 survivors increased from 8 to 1066. The number of ouabain-resistant mutants per 10^6 survivors increased in much the same manner until concentrations greater than 13 M were reached. Higher concentrations tended to have a cytotoxic effect on these cells. 2-Chloroacetaldehyde produced similar results in concentrations up to 6.4 μ M. Increasing concentrations exhibited strong cytotoxicity. 2-Chloroethanol and monochloroacetic acid, the urinary end-products of vinyl chloride metabolism, had little effect on cloning efficiency, and accounted for few ouabain or 8-azaguanine mutants. Chloroethylene oxide caused a mutagenic response with a much lower toxicity as compared to that of 2-chloroacetaldehyde at equimolar concentrations. Thus, 2-chloroethylene oxide acts as a mutagen *per se* and not exclusively *via* its spontaneous rearrangement product 2-chloroacetaldehyde.

- 4903 EXPERIMENTAL ACUTE TOXICITY OF VINYL CHLORIDE (MONOCHLOROETHENE). (Eng.) Prodan, L. (Inst. Med. Pharm., Cluj, Rumania); Suciu, I.; Pislaru, V.; Ilea, E.; Pascu, L. *Ann. NY Acad. Sci.* 246:154-158; 1975.

The effects of acute vinyl chloride poisoning were studied in mice, rats, guinea pigs, and rabbits. The animals were placed in gas chambers and exposed for two hours to varying concentrations of vinyl chloride (107.25-700 mg/l). The lethality of the gas was decreased by ventilation, indicating that vinyl chloride is an inert gas with no tendency to diffuse. The LD₅₀ for mice was 11.50-12.00%, 293.75 mg/liter, or 27,419 ppm; the LD₁₀₀ was 139,975 ppm. The LD₅₀ and LD₁₀₀ values, respectively, were 47,640 ppm and 208,425 ppm for rats,

236,215 ppm and 277,900 ppm for guinea pigs, and 236,215 ppm and 277,900 ppm for rabbits. The most common symptom in all exposed animals was a state of narcosis proceeding from excitement to tranquility and finally to falling down. Narcosis generally occurred during the first hour. Other symptoms included intense salivation and lacrimation, muscular contractions and tonico-clonic convulsions, accelerated respiration, bradypnea, respiratory failure, intense cyanosis, and conjunctival congestion. The animals died with general convulsions, respiratory failure, exophthalmia, and deflection of the head on the abdomen. Muscular contractions were more prominent in the rabbits and guinea pigs than in the mice and rats, and the rabbits showed heavy respiration, salivation, and contractions during narcosis. The animals that survived two hours of exposure rapidly regained a normal appearance. Autopsy revealed general congestion of all internal organs, and some animals showed pulmonary edema, marmorated liver, and slight congestion of the kidneys.

- 4904 SPECIFICITY OF MUTAGENIC CHEMICAL CARCINOGENS. (Eng.) de Serres, F. J. (Nat'l. Inst. Environ. Health Sci., Research Triangle Park, N.C.). *Mutat. Res.* 29(2):293; 1975.

- 4905 DNA DAMAGE AND REPAIR *IN VIVO*--A MEASUREMENT OF *IN VIVO* CARCINOGEN-DNA INTERACTION AND A POSSIBLE BIOASSAY FOR CARCINOGENS. (Eng.) Sarma, D. S. R. (Temple Univ. Sch. Medicine, Philadelphia, Pa.); Zubroff, J.; Michael, R. O.; Rajalakshmi, S. *Proc. Int. Cancer Congr. 11th.* Vol. 2. (Chemical and Viral Oncogenesis). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 82-86.

- 4906 ENHANCEMENT OF VIRAL TRANSFORMATION, INDUCTION OF DNA SINGLE-STRAND BREAKS AND REPAIR SYNTHESIS BY CHEMICAL CARCINOGENS IN HAMSTER CELLS [abstract]. (Eng.) Casto, B. (BioLabs, Inc., Northbrook, Ill.); Pieczynski, W.; Janosko, N.; DiPaolo, J. *Proc. Am. Assoc. Cancer Res.* 16:83; 1975.

- 4907 CONFORMATIONAL AND FUNCTIONAL CHANGES IN NUCLEIC ACIDS INDUCED BY CHEMICAL CARCINOGENS. (Eng.) Weinstein, I. B. (Inst. Cancer Res., Columbia Univ., New York, N.Y. 10032); Grunberger, D.; Blobstein, S. *Proc. Int. Cancer Congr. 11th.* Vol. 2 (Chemical and Viral Oncogenesis). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 47-53.

- 4908 CHLORAMPHENICOL COMPETITION WITH N-2-FLUORENYLDIACETAMIDE FOR BINDING SITES IN NUCLEAR DNA OF RATS. (Eng.) Firminger, H. I. (Univ. Maryland Med. Sch., Baltimore); Kim, K. M.; Morrison, D. M. *Fed. Proc.* 34(3):871; 1975.

- 4909 METABOLISM AND DISPOSITION OF N-[4-(5-NITRO-2-FLURYL)-2-¹⁴C-THIAZOLYL]ACETAMIDE (NFTA-¹⁴C) IN RAT. (Eng.) Chiu, C. W. (Univ. Wisconsin Med. Sch., Madison); Wang, C. Y.; Bryan, G. *T. Fed. Proc.* 34(3):664; 1975.
- 4910 PROTEINS WHICH SPECIFICALLY BIND CARCINOGENS. (Eng.) Ketterer, B. (Courtauld Inst. Biochemistry, Meddlesex Hosp., London, WIP 5PR, U.K.); Tipping, E.; Beale, D.; Meuwissen, J.; Kay, C. M. *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 25-29.
- 4911 METABOLIC REDUCTION OF BENZIDINE AZO DYES TO BENZIDINE IN THE RHESUS MONKEY. (Eng.) Rinde, E. (New York Univ. Med. Cent., N.Y.); Troll, W. *J. Natl. Cancer Inst.* 55(1):181-187; 1975.
- 4912 IMPROVEMENT OF SCREENING METHODS OF CHEMICAL CARCINOGENS USING MICROBES [abstract]. (Jpn.) Yahagi, T. (Cancer Center Res. Inst., Tokyo, Japan); Nagao, M.; Seino, Y.; Matsushima, T.; Sugimura, T. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 27.
- 4913 CARCINOGENESIS IN TISSUE CULTURE 83: ATTEMPTS TO TRANSFORM HUMAN CELLS IN CULTURE WITH CHEMICAL CARCINOGENS [abstract]. (Jpn.) Namba, M. (Kawasaki Medical Sch., Kurashiki, Japan); Kimoto, T. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 25.
- 4914 CARCINOGENESIS IN TISSUE CULTURE 85: TRANSPLACENTAL IN VIVO-IN VITRO CHEMICAL CARCINOGENESIS [abstract]. (Jpn.) Inui, N. (Cytogenet. Inst. Expt. Biol., Hadano, Kanagawa, Japan); Nishi, Y.; Kondo, M. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 25.
- 4915 SPECIES DIFFERENCES IN N-HYDROXYLATION OF AMINOAZO DYES (II.) (Jpn.) Takahashi, A. (Natl. Inst. Hygienic Sci., Tokyo, Japan); Omori, Y.; Sodemoto, Y.; Enomoto, M.; Sato, K. *Gann, Proc. Jpn. Cancer Assoc., 34th Meeting, October 1975.* p. 35.
- 4916 ANALYTICAL STUDY ON THE ROLE OF CARBON TETRACHLORIDE (CCl₄) IN THE MECHANISM OF AZO DYE HEPATOCARCINOGENESIS IN RATS [abstract]. (Jpn.) Kanematsu, T. (Cancer Res. Inst., Kyushu Univ., Fukuoka, Japan); Baba, T. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 35.
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See also:

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- * (Phys): 4990, 4997
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- * (Immun): 5077, 5078, 5088, 5108, 5138, 5148, 5149, 5162, 5166, 5174
- * (Path): 5182, 5218, 5236
- * (Epid-Biom): 5277, 5285, 5286, 5287, 5288, 5290, 5294, 5298, 5300

- 4987 BREAST CANCER AND BASALOMA DEVELOPING AFTER RADIATION THERAPY OF THE ANTERIOR THORACIC WALL FOR HEMANGIOMA. (Rus.) Knyrov, G. G. (Moscow Science Res. Inst. Roentgenology Radiology, Moscow, U.S.S.R.); Podliashchuk, E. L.; Kozlovskii, O. M. *Med. Radiol. (Mosk.)* 20(3):75-78; 1975.

Intraductal cancer of the right breast with transition into invasive adenocarcinoma, and basal cell carcinoma of the skin on the right side of the chest were diagnosed in a 26-yr-old woman who had received intense radiotherapy for a large hemangioma of the right side of the chest in early childhood. She was first given gamma-therapy (1,100 rads) at the age of eight months, followed by orthovoltage x-ray therapy (dose unknown) one month later, and by radium therapy (158.2 mg, 94 rads/hr, irradiated surface 54.6 cm², 9-10 hr/day, total duration 32 hr) at the age of two years. Regression of the hemangioma, normal development but hypoplasia of the right breast were observed after the completion of the radiotherapy. Subtotal thyroidectomy was performed for nodular goiter at the age of 16 yr. Both the struma, basal cell carcinoma, and the breast cancer are considered as being related to the radiotherapy. The findings indicate that bones, breast area, and endocrine glands should not be irradiated in children with hemangioma, and irradiation should be performed with caution.

- 4988 RADIATION-INDUCED CHROMOSOMAL ABERRATIONS IN HUMAN LYMPHOCYTES AFTER PARTIAL-BODY EXPOSURE TO ⁶⁰CO GAMMA IRRADIATION AND *IN VITRO* EXPOSURE TO 230 kV X-IRRADIATION. (Eng.) Watson, G. E. (Medical Res. Council, Radiobiology Unit, Harwell, Didcot, Berks OX11 0RD, England); Gillies, N. E. *Br. J. Radiol.* 48(570):487-493; 1975.

Chromosome aberrations in first division cells were measured in blood samples from 12 patients having a single partial-body x-ray exposure to different anatomical sites. Blood samples were obtained at various times, up to three days, after single partial-body therapeutic exposure ranging from 75-100 rads of ⁶⁰Co γ-irradiation. Small yields of chromosome aberrations were present in lymphocytes from the 12 patients at the first metaphase in culture. When all patients were considered there was no correlation between treatment dose and aberration frequency, but on subdivision into two groups on the basis of whether the reticuloendothelial system was involved in the cancer, linear regression analysis could be fitted to the data for each group. An *in vitro* dose-response curve for dicentric induced by 230 kV X rays at a dose rate of 23.3 rads/min was constructed for use as a standard calibration curve for 48-hr cultures. The yield of dicentric aberrations was best fitted by a power law model, $Y = kD^n$ in which $k = (1.59 \pm 0.66) \cdot 10^{-4}$ and $n = 1.49 \pm 0.08$, ($P = 0.96$). Lower yields of chromosome-type aberrations were found in the peripheral blood of patients receiving partial-body irradiation as compared with the yields induced by similar *in vitro* doses of radiation; this may

be attributed to a combination of factors: (a) the dilution of irradiated lymphocytes by nonirradiated cells during lymphocyte recirculation, and (b) the greater likelihood of the division of unirradiated than irradiated cells, thereby reducing the observed yield of aberrations in a mixture. Thus, the standard *in vitro* dose response curve probably does not represent the *in vivo* situation.

- 4989 TOTAL-BODY IRRADIATION AND HUMAN CHROMOSOMES. IV. CYTOGENETIC FOLLOW-UP STUDIES 8 AND 10 1/2 YEARS AFTER TOTAL-BODY IRRADIATION. (Eng.) Goh, K. (Med. Div., Oak Ridge Assoc. Univ., Tenn.). *Radiat. Res.* 62(2):364-373; 1975.

The metaphase chromosomes from six men exposed to total body irradiation of 22.8-365 rads were studied 8 and 10.5 yr after irradiation. Metaphases were obtained either from cultured peripheral blood WBC (three days, 37 C), or from cultured bone marrow cells. Eight years after irradiation, there were 12.2% abnormal cells found in 1,682 metaphases of four of the six patients; this was compared to 2% found in the 1,100 metaphases from cultures of five controls. The more frequent abnormalities were fragments, translocations, and small G chromosome. Bone marrow specimens from five patients revealed 18.8% abnormal cells in 500 metaphases. After 10.5 yr, 17.4% of 447 metaphases were abnormal, as compared to 5.5% of 550 metaphases of normal donors. The same types of abnormalities had been found in the same patients in previous studies made 2.5, 3.5, and 7 yr after exposure. There is good evidence that there is an increased incidence of cancer and leukemia among populations exposed to radiation. It has been suggested that chromosomal aberrations are involved in the development of some cancer or leukemia in irradiated persons. However, none of the patients had these diseases. It is possible that the development of clinical cancer or leukemia depends not only on the presence of abnormal cells, but also, on factors that give advantage to these abnormal cells.

- 4990 POSTREPLICATION REPAIR OF DNA CONTAINING PSORALEN ADDITION PRODUCTS IN CHINESE HAMSTER CELLS. (Eng.) Ben-Hur, E. (Hadassah Medical Sch., Jerusalem, Israel); Elkind, M. M. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 170-175.

The postreplication repair of DNA containing psoralen addition products was studied in V79 Chinese hamster fibroblasts, subline V79-753B-3M. Monolayer cultures were treated with 1×10^{-6} M 4,5',8-trimethylpsoralen and near ultraviolet (NUV) light (10 ergs/mm²-sec, with the maximum intensity at 320 nm). The cell survival curve was typical of the damage accumulation type, and the repair of sublethal psoralen + NUV damage was shown to go to completion. The lethal effect was due mainly to crosslinks, the crosslinking rate, in a two-step photoinduction process, being rate limiting.

The reduction in the proportion of DNA that did not renature was a function of NUV exposure in the presence of psoralen, and the ability of cells treated with psoralen + NUV light to synthesize DNA decreased in a dose-dependent manner. The rate of inhibition of 80-90% of the DNA appeared to require a single-hit exposure of 0.6-1.0 min, while 10-20% of the DNA required an exposure of 9-10 min. The DNA synthesized after psoralen + NUV was smaller than the DNA from untreated cells as indicated by its sedimentation rate in alkaline sucrose gradients. A linear relationship was obtained between the reduction in DNA size and NUV exposure. The reduction in DNA size appeared to parallel the binding of psoralen, and crosslinks were more efficient than monoadducts in reducing the size of newly synthesized DNA. Examination of pulse-labeled cells after a chase period without [³H]-thymidine indicated that the DNA synthesized in cells exposed to psoralen + NUV increased in size, but more slowly than that synthesized in untreated cells. The results suggest that in cells exposed to psoralen + NUV, semiconservative DNA replication results in gaps in the nascent DNA opposite photoproducts in the template strand. According to this model, the increase in DNA size observed during the chase period represents a postreplication repair of the DNA.

- 4991 EXPERIMENTAL MODIFICATION OF PHOTOCARCINOGENESIS. I. FLUORESCENT WHITENING AGENTS AND SHORT-WAVE UVR. (Eng.) Forbes, P. D. (Temple Univ. Health Sci. Cent., Philadelphia, Pa.); Urbach, F. *Food Cosmet. Toxicol.* 13(3):335-337; 1975.

This study documents the development of methods for evaluating the interaction of UVR and chemicals in skin carcinogenesis and compares the ability of FWAs and psoralens to influence UVR photocarcinogenesis. Erythema was produced on the skin of hairless mutant (HRS/J) mice by a single exposure to low-pressure mercury-vapour (germicidal) ultraviolet lamps. The acute reaction was not affected by pretreatment of the skin with 20 µg of a fluorescent whitening agent (FWA), disodium 4,4'-bis-(4,6-dianilino-1,3,5-triazin-2-yl)-aminostilbene-2,2'-disulphonate, applied topically in 20 µl methanol. Skin tumours were produced in hairless mice during several months of daily exposure to the same lamps. Slightly fewer tumours, with a slightly longer latent period, were produced in mice similarly irradiated but pretreated daily with FWA as above. Thus, under the test conditions used, the FWA was not phototoxic, nor did it enhance photocarcinogenesis.

- 4992 RADIATION RISKS FROM MAMMOGRAPHY: A PRELIMINARY REPORT. (Eng.) Crosby, E. H. (No affiliation given); Ty, J. *Guthrie Bull.* 44(3): 133-139; 1975.

- 4993 RADIONUCLIDES IN THE AUTOPSY SAMPLES FROM THOROTRAST PATIENTS. (Eng.) Molla, M. A. R. (Health Phys. Div., At. Energy Cent., Dacca, Bangladesh). *Health Phys.* 28(3):295-297; 1975.

- 4994 THE RELATION BETWEEN JUVENILE CANCER AND OBSTETRIC RADIOGRAPHY. (Eng.) Holford, R. M. (Health Phys. Branch, At. Energy Canada Ltd., Chalk River Nuclear Lab., Ontario, Canada). *Health Phys.* 28(2):153-156; 1975.

- 4995 DEVELOPMENT OF MALIGNANT NEOPLASIAS AFTER REPEATED RADIOTHERAPY. (Rus.) Fishbein, A. V. (Dept. Pathoanat., Lvov Med. Inst., Lvov, U.S.S.R.); Iampol'skaia, S. A. *Vopr. Onkol.* 21(2): 103-104; 1975.

- 4996 ON TUMORS OF SOFT TISSUES AND INTERNAL ORGANS IN NEPTUNIUM-237 INDUCED LESIONS. (Rus.) Levdivik, T. I. (No affiliation given); Buldakov, L. A. *Vopr. Onkol.* 21(1):80-87; 1975.

- 4997 EFFECT OF LOW DIETARY CALCIUM ON CHRONIC CADMIUM TOXICITY (Eng.) Washko, P. W. (Dept. Nutr., Rutgers Univ., New Brunswick, N.J.); Cousins, R. J. *Nutr. Rep. Int.* 11(2):113-128; 1975.

See also:

- * (Rev): 4806, 4830, 4831, 4832
- * (Chem): 4920
- * (Viral): 5052
- * (Immun): 5090, 5102, 5129
- * (Path): 5181, 5189, 5225, 5263
- * (Epid-Biom): 5290

- 4998 ENDOGENOUS AGENTS IN PRIMARY CELL CULTURES WITH SPECIAL REFERENCE TO LATENT VIRUSES. (Eng.) Swack, N. S. (Veterans Administration Hosp., West Haven, Conn. 06516); Hsiung, G. D. *In Vitro* 10(5/6):260-267; 1974.

A longitudinal survey was conducted of the prevalence of endogenous viruses in primary cell cultures prepared from primate and nonprimate tissues. Detection of endogenous virus was accomplished primarily by holding the cultures for long-term incubation while testing for virus-induced cytopathic effect, hemadsorption, and staining with hematoxylin and eosin for virus-induced cellular inclusions. Fluorescent antibody staining was used for the detection of green monkey cytomegalovirus (CMV) in green monkey kidney cells, for rabbit Herpes-like virus (HLV) in rabbit kidney cells, and for bovine virus diarrhea (BVD) in bovine embryo kidney cells. Tests for the presence of C-type virus in some cultures were performed by electron microscope examination of 5-bromo-2-deoxyuridine-treated cells. Cultures prepared from rhesus and green monkeys contained the greatest variety of virus isolates. Foamy virus was present in 28% of the rhesus and 10% of the green monkey cultures. Twenty percent of the rhesus cultures were infected with simian virus 40 (SV40) and an additional 3% were infected with both SV40 and foamy virus. Of the green monkey cultures, 10% showed infection with SV40 and 8% were infected with DMV. Almost all strain 2 guinea pig cultures contained LHLV, and both strain 2 and Hartley strain cultures contained C-type virus. Bovine embryo and rabbit kidney cell cultures were rarely infected with viruses, but BVD antigen and HLV antigen were demonstrated in these cultures. Only 3% of 144 human embryo cultures were positive for viruses (one measles, one CMB, and two adenovirus isolates). *Toxoplasma gondii* infection was noted in one lot of Hartley guinea pig kidney cell cultures and microfilariae in one lot of green monkey kidney cell cultures. It is noted that the screening of animals, by testing for the presence of neutralizing antibody, was not an effective procedure in selecting virus-free animals for cell culture purposes.

- 4999 THE REPLICATION OF ADENO-ASSOCIATED SATELLITE VIRUS. THE THREE-COMPONENT SYSTEM, SATELLITE, HERPES VIRUS, AND ADENOVIRUS. (Eng.) Mayor, H. D. (Baylor Coll. Medicine, Houston, Tex. 77025); Drake, S.; Jordan, L. *J. Ultrastruct. Res.* 52(1):52-63; 1975.

The nature and properties of the viral products produced in tissue culture cells infected with adeno-associated satellite virus, (ASV) adenovirus, and herpes simplex virus were studied. The viruses were capable of replication in cultures coinfecting with all three viruses. Satellite virus demonstrated an influence on the synthesis of adenovirus structural proteins when cultures that had been inoculated simultaneously with satellite virus and herpes virus were challenged 12 hr later with adenovirus. Adenovirus structural antigens were detected by immunofluorescence within an additional four hr in these cultures. These antigens normally are not seen un-

til 10-12 hr after infection. Infectious satellite virus was not isolated until its normal time of appearance 12 hr later, when it was detectable by complement fixation and by immunofluorescence. Immune electron microscopy indicates that an adenovirus-coded protein, possibly one involved in the attachment of fiber to pentaon may be involved in satellite maturation.

- 5000 PHYSICAL MAPPING OF TEMPERATURE-SENSITIVE MUTATIONS OF ADENOVIRUSES. (Eng.) Sambrook, J. (Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, N.Y.); Williams, J.; Sharp, P. A.; Grodzicker, T. *J. Mol. Biol.* 97(3):369-390; 1975.

Temperature-sensitive mutants of the adenovirus 2-simian virus 40 hybrid, Ad2⁺ND1, were isolated and crossed with temperature-sensitive mutants of adenovirus type 5 (Ad5). Forty-five wild type recombinants were selected, and their DNAs were separately digested with five restriction endonucleases, *EcoRI*, *HpaI*, *BamI*, *HindIII*, and *SmaI*. Fifteen sites cleaved by these enzymes were unique to one parental DNA or the other. The fragments obtained by digestion of each of the recombinant DNAs were separated by gel electrophoresis and compared with those obtained from the parental genomes. The recombinant DNAs consisted of sequences derived both from Ad5 and from Ad2⁺ND1. Knowing the positions at which the five restriction enzymes cleaved the genomes of the parental it was possible to decide which regions of each recombinant DNA were composed of Ad5 and which were composed of Ad2⁺ND1 sequences.

- 5001 GENES FOR VA-RNA IN ADENOVIRUS 2. (Eng.) Matthews, M. B. (Cold Spring Harbor Lab., P.O. Box 100, Cold Spring Harbor, N.Y. 11724). *Cell* 6(2):223-229; 1975.

The genetic coding for the virus-associated RNA (VA-RNA) of adenovirus 2 (Ad2) was studied. The VA-RNA species within Ad2-infected cells were identified by digestion of the VA-RNA with T1 ribonuclease and two-dimensional paper electrophoresis. The location of the VA-RNA genes was then determined by agarose electrophoresis following digestion of the Ad2 DNA with six restriction enzymes. Agarose gel electrophoresis, blotting on nitrocellulose paper, hybridization, and enzyme digestion were also used to determine the direction of transcription, fine structure mapping, and fingerprinting of the VA-RNAs. The results indicate that the VA-RNA from Ad2-infected cells consists of two species. The gene coding for the major species mapped at position 30 on the viral DNA, where it spanned a site cleaved by the restriction enzyme *Bam* HI. The minor species, which constituted a small amount of the total VA-RNA, was distantly related in oligonucleotide composition to the major species. Its template mapped within 700 base pairs to the right of the gene for the major species. The direction of transcription was from left to right on the conventional Ad2 map. The minor species had an apparent size of 150 nucleotides. The fingerprint of this species contained 19-22 spots, of which

8-11 were also present in fingerprints of the major species; only four spots containing oligonucleotides of four or more bases were common to both species, however. It is concluded that the differences between the two VA-RNA species are extensive, possibly indicating the divergence of the two sequences at an early stage in adenovirus evolution. VA-RNA may be involved in the regulation of adenovirus gene expression late in infection.

- 5002 TRANSCRIPTION OF THE GENOME OF ADENOVIRUS TYPE 12: VIRAL mRNA IN PRODUCTIVELY INFECTED KB CELLS. (Eng.) Scheidtmann, K.-H. (Institut für Genetik der Universität zu Köln, D-5000 Köln-Lindenthal, Weyertal 121, West Germany); Ortin, J.; Doerfler, W. *Eur. J. Biochem.* 58(2): 283-290; 1975.

Virus-specific, polysome-associated messenger RNA was investigated early and late after infection of human KB cells with adenovirus type 12. The cells were incubated for two hours at 37 C to allow virus adsorption. At different times after infection, the infected cells were pulse-labeled with 6-[³H]-thymidine (20 µCi/ml) for two hours. The total intracellular DNA from [³H]thymidine-labeled adenovirus 12-infected KB cells was extracted by the dodecylsulfate/pronase/phenol method, and the percentage of viral DNA was assessed by the DNA-DNA filter hybridization procedure. The RNA of adenovirus 12-infected KB cells was pulse-labeled 6-8 hr or 26-28 hr after infection, and the cells were subsequently fractionated into nuclei and cytoplasm. The polysomes were isolated from the cytoplasm by velocity sedimentation on 7-47% sucrose density gradients. By affinity chromatography on poly(uridylic acid)-Sephadex, the polysomal RNA was subfractionated into polyadenylated and nonpolyadenylated RNA. The amounts of adenovirus 12-specific sequences in both the polyadenylated and nonpolyadenylated RNA fractions were determined by saturation hybridization. The size of the polysome-associated adenovirus 12-specific messenger RNA synthesized in KB cells early and late after infection with adenovirus 12 was measured by zonal sedimentation in sucrose density gradients and by polyacrylamide gel electrophoresis in the presence of 98% formamide. The data indicated that adenovirus 12 synthesis started between 12-14 hr after infection, with a concomitant turn-off of cellular DNA synthesis. Most of the viral messenger RNA was polyadenylated and accounted for 0.46% and 24.1% of the messenger RNA synthesized early and late after infection, respectively; the corresponding values for the nonpolyadenylated RNA were 0.09% and 4.2%, respectively. Sixty-eight percent of the adenovirus 12-specific RNA labeled early and 86% labeled later after infection were polyadenylated. The viral-specific messenger RNA isolated both early and late after infection fell into several size-classes, 0.3×10^6 - 1.5×10^6 for the early RNA and 0.6×10^6 - 2.3×10^6 for the late RNA. It is suggested that if each size-class of viral messenger RNA corresponded to a unique species of messenger RNA, then early in infection about 45% of the viral genome is expressed, while late in infection about 70% of the genome is transcribed.

- 5003 ADENOVIRUS GENE FUNCTION REQUIRED FOR INDUCTION OF NUCLEAR ACIDIC PROTEIN SYNTHESIS: BINDING OF THESE PROTEINS TO ADENOVIRUS DNA. (Eng.) Ledinko, N. (Dept. Biology, Univ. Akron Akron, Ohio 44325). *J. Virol.* 16(4):807-817; 1975.

The role of the nuclear acidic proteins in adenovirus-infected human embryo kidney (HEK) cells was studied, as was the interaction of adenovirus 12 (H12) DNA with the nuclear acidic protein fraction isolated from H12-infected HEK cells. The ³H- or ¹⁴C-labeled nuclear and cytoplasmic acidic proteins of infected and mock-infected cells were separated by electrophoresis on sodium dodecyl sulfate polyacrylamide gels. In some cases, the H12-infected cultures were treated with actinomycin D (2 µg/ml), after which they were labeled. In other experiments, infected HEK cells were treated with 1-β-D-arabinofuranosylcytosine (ara-C) (20 µg/ml) prior to the addition of ³H. The interaction of the H12 DNA with the nuclear acidic protein fraction isolated from the H12-infected cells was determined by a membrane filter technique. Two different viral DNA-defective temperature-sensitive mutants of H12 (ts401 and ts406) were defective in their ability to induce nuclear acidic protein synthesis (both virion and nonvirion components) after lytic infection of HEK cells at the restrictive temperature (31 C). Treatment of the infected cells with actinomycin D suppressed the synthesis of other classes of nuclear nonvirion acidic proteins during the subsequent late maturation period. Measurements of the ability of different DNA preparations to inhibit the H12 DNA-acidic protein complex formation suggested that the nuclear acidic proteins bound to native H12 or HEK cell DNA with much higher affinity than to native calf thymus DNA. Moreover, native H12 DNA was able to bind the acidic proteins more efficiently than was denatured H12 DNA. The acidic proteins isolated from the cytoplasm of H12-infected cells bound approximately 100-fold less to native H12 DNA than did the nuclear proteins. Furthermore, the H12 DNA binding affinity of the nuclear acidic proteins from uninfected cells, or from ara-C-treated cells, was somewhat lower than that of the nuclear proteins from infected, untreated cells. The data support the hypothesis that some of the induced nuclear acidic proteins have a regulatory function concerned with late events in productive adenovirus infection.

- 5004 MICROVESICLES AND VESICLES OF MULTIVESICULAR BODIES VERSUS "VIRUS-LIKE" PARTICLES. (Eng.) Dalton, A. J. (Nat'l. Cancer Inst., Bethesda, Md. 20014). *J. Nat'l. Cancer Inst.* 54(5):1137-1148; 1975.

Pellets obtained by centrifugation of unfiltered or filtered fetal bovine serum (FBS) were examined with the electron microscope. Many large, dense bodies, small particles, and rodlike bodies were present. Higher magnification revealed particles with a trilaminar membrane and moderately electron-dense core. Clumps of extra-cellular microvesicles were found frequently associated with the cells of suspension cultures derived from human solid tumors, including T-24, T-27, T-40, and T-55A. Vesicles of

multivesicular bodies and microvesicles possessed the same structure and size range as the serum microvesicles. Numerous microvesicles were also present with cell debris in the lumen of acini of the normal baboon prostate. Although the vesicles of multivesicular bodies and extracellular microvesicles had a similar ultrastructure, there was no evidence to suggest an identical origin. Microvesicles occurred near the cell surface of lymphoblastoid cells, and were occasionally phagocytosed into large and complex vacuoles. These microvesicles originated from the breakdown products of normal cell components. In addition to the microvesicles present in FBS, others have been derived from degenerating mitochondrial cristae. The release of bodies with the ultrastructure of microvesicles from a ruptured mitochondrion further evidenced the origin of microvesicles from degenerating mitochondria.

- 5005 ONCORNAVIRUS-LIKE PARTICLES IN HUMAN SKIN CANCERS. (Eng.) Balda, B.-R. (Dept. Dermatology, Univ. Munich, 8 Munich 2, Frauenlobstr. 9, Germany); Hehlmann, R.; Cho, J.-R.; Spiegelman, S. *Proc. Natl. Acad. Sci. USA* 72(9):3697-3700; 1975.

Tissue specimens from 14 cases of human melanoma were examined for the presence of virus-like particles. Specimens were homogenized and repeatedly centrifuged (4000 x g and 10,000 x g, for ten minutes at 0-2 C each, 100,000 x g at 4 C for one hour) and then usually suspended in 50 l 10 mM Tris-HCl/0.1 ml tissue, and assayed for 70S RNA and reverse transcriptase, but occasionally the specimens were further density centrifuged (27,000 rpm at 4 C for 180 min) and the density region (1.16-1.19 g/ml) with the highest polymerase activity was collected and assayed. Cellular RNA was extracted by a similar process. Tritiated DNA was synthesized by the particles in an endogenous reaction; the DNA hybridized to RNA from the melanoma particulate structures but not to RNA from normal skin. The RNA from melanoma particles is distinguishable by hybridization from the RNA in similar particles, which also contain RNA and enzyme, found in basal and squamous cell carcinomas.

- 5006 MURINE INTRACISTERAL TYPE A PARTICLES: A BIOCHEMICAL CHARACTERIZATION. (Eng.) Wong-Staal, F. (Natl. Cancer Inst., Bethesda, Md. 20014); Reitz, M. S., Jr.; Trainor, C. D.; Gallo, R. C. *J. Virol.* 16(4):887-896; 1975.

The intracisternal A particle preparations from a murine neuroblastoma cell line (N18) and a mineral oil-induced murine plasmacytoma (MOPC-104E) were biochemically characterized. RNA was prepared from the A-particle preparations by incubation with pronase and 1% sodium dodecyl sulfate. Radiolabeled A-particle DNA transcripts of endogenous nucleic acid (cdNA) were synthesized from endogenous reactions from disrupted A-particles and by synthesis from reactions using avian myeloblastosis virus (AMV) and purified RNA from A-particles. The A-particles were analyzed using sucrose velocity gradients, and the A-particle RNA and poly(A) were ana-

lyzed by polyacrylamide gel electrophoresis. Oligo-(dT)-cellulose chromatography, molecular hybridization of ³H-labeled DNA to RNA, and DNA polymerase assays were also carried out. The intracisternal A-particle preparations from the N18 and MOPC-104E cells both contained an endogenous RNA-dependent DNA polymerase activity and high molecular-weight polyadenylic acid (poly(A))-containing RNA. The DNA polymerase activity was stimulated by oligo-(dG) x poly(C), oligo(dT) x poly(A), and, to a lesser extent, by oligo(dT) x poly(dA). The high-molecular-weight RNA was predominantly 35S and contained a poly(A) tract of approximately 220 nucleotides, as judged by polyacrylamide gel electrophoresis. Small amounts of 70S RNA were also present. This preparation contained RNA homologous to the RNA from type-C particles, as judged by the molecular hybridization experiments. However, since this RNA was derived only in part from the A-particles and in part from other cellular RNA, hybridization of A-particle endogenously-synthesized DNA or the reverse transcripts of A-particle RNA to purified type C virus 70S RNA may more accurately reflect the relationship of A-particle RNA to C-particle RNA. None of these DNA transcripts hybridized significantly to C-particle 70S RNA, although MOPC and N18 DNA transcripts share significant homology. It is concluded that murine intracisternal A particles are not closely related genetically to the tested murine type C viruses. It is possible, however, that all the A-particle DNA transcripts are copied from only a small part of the genome that is unrelated to C-particle RNA.

- 5007 COMPARATIVE STUDIES ON THE STRUCTURAL PHOSPHOPROTEINS OF MAMMALIAN TYPE C VIRUSES. (Eng.) Pal, B. K. (Univ. Southern California Sch. Medicine, Los Angeles, Calif. 90033); McAllister, R. M.; Gardner, M. B.; Roy-Burman, P. *J. Virol.* 16(1):123-131; 1975.

The major phosphoproteins of mammalian type C viruses were comparatively studied. Virion phosphoproteins were fractionated, subjected to sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis and analyzed by urea-polyacrylamide gel electrophoresis; the polyamino acids were identified *via* HCl hydrolysis. Molecular weights were estimated by guanidine-agarose chromatography and relative electrophoretic mobility in SDS. The polypeptide p12 was found to be the major phosphoprotein common to primate-derived woolly monkey sarcoma virus (SSV-1/SSAV-1), gibbon ape lymphosarcoma virus (GaLV), and to type C viruses of lower mammalian species, including mouse (AT-124), rat, and cat; the endogenous cat virus (RD-114) was the noted exception. The endogenous mouse virus was deficient in p15, while the endogenous baboon virus (BKD) lacked p12. High voltage electrophoresis identified the major phosphoamino acid as *o*-phosphoserine for p12 of AT-124, and phosphothreonine for BKD p15 and RD-114 p15. GaLV contained both phosphoserine and phosphothreonine. In addition to p12, a second major phosphoprotein of 10,000 molecular wt was found only in rat type C viruses and the Kristin mouse sarcoma virus. In addition to evidence that mammalian type C viruses contain phosphoproteins as their structural components,

an evolutionary relationship between woolly monkey or gibbon ape virus and mouse type C viruses is suggested. Because the phosphorylated proteins were present in the virion structure in several different but nonrandom phosphorylated states, it is suggested that the various levels of phosphorylation relate to the assembly of virus structural components.

- 5008 INTERACTIONS OF CHEMICAL INDUCERS AND STEROID ENHANCERS OF ENDOGENOUS MOUSE TYPE-C RNA VIRUSES. (Eng.) Dunn, C. Y. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Aaronson, S. A.; Stephenson, J. R. *Virology* 66(2):579-588; 1975.

The effects of halogenated pyrimidines and inhibitors of protein synthesis were compared on cells of genetic crosses involving BALB/c, C58, and NIH Swiss mouse strains. Cycloheximide was found to activate xenotropic virus from those genetic crosses from which xenotropic virus was inducible by iodo-deoxyuridine. In contrast, NIH Swiss-tropic endogenous viruses of BALB/c and C58 cells were much more resistant to activation by inhibitors of protein synthesis. Steroids possessing glucocorticoid activity enhanced virus release by cells exposed to either class of inducers. Unlike the inducers, which inhibited type-C virus release by exogenously infected cells, steroids augmented chronic virus production. These findings indicate that the mechanisms of action of inhibitors of protein synthesis and halogenated pyrimidines involve the virus-activation process, while steroids enhance rather than initiate virus synthesis.

- 5009 STRUCTURE, SUBUNIT COMPOSITION, AND MOLECULAR WEIGHT OF RD-114 RNA. (Eng.) Kung, H.-J. (Childrens Hosp. Los Angeles, Los Angeles, Calif. 90054); Bailey, J. M.; Davidson, N.; Nicolson, M. O.; McAllister, R. M. *J. Virol.* 16(2):397-411; 1975.

The properties and subunit composition of the RNA extracted from RD-114 virions were studied. The RNA extracted from the virion was found to have a sedimentation coefficient of 52S in a nondenaturing aqueous electrolyte. The estimated molecular weight by sedimentation in nondenaturing and weakly denaturing media was in the range 5.7×10^6 to 7.0×10^6 . By electron microscopy, under moderately denaturing conditions, the 52S molecule was seen to be an extended single strand with a contour length of about $4.0 \mu\text{m}$ corresponding to a molecular weight of 5.74×10^6 . It contained two characteristic secondary structure features: (a) a central Y- or T-shaped structure (the rabbit ears) with a molecular weight of 0.3×10^6 ; and (b) two symmetrically disposed loops on each side of and at equal distance from the center. The 52S molecule consisted of two half-size molecules, with molecular weight 2.8×10^6 , joined together within the central rabbit ears feature. Melting of the rabbit ears, with concomitant dissociation of the 52S molecule into subunits, was caused by either one of two strongly denaturing treatments: incubation in a mixture of $\text{CH}_3\text{H}_2\text{OH}$ (10 mM) and glyoxal (1 M) at room temperature, or thermal dissociation in a urea-formamide (8 M urea/1 formamide) solvent. When

half-size molecules were quenched from denaturing temperatures, a new off-center secondary structure feature (designated "branch-like" structure) was seen. The dissociation behavior of the 52S complex and the molecular weight of the subunits were confirmed by gel electrophoresis. The loop structures melted at fairly low temperatures; the dissociation of the 52S molecule into its two subunits occurred at a higher temperature corresponding to a base composition of about 63% guanosine plus cytosine. Polyadenylic acid mapping by electron microscopy showed that the 52S molecule contained two polyadenylic acid segments, one at each end. It thus appears that 52S RD-114 RNA consists of two 2.8×10^6 dalton subunits, each with a characteristic secondary structure loop, and joined at the 5' ends to form the rabbit ears secondary structure feature. The observations are consistent with, but do not require, the conclusion that the two 2.8×10^6 dalton subunits of 52S RD-114 RNA are identical.

- 5010 SPLEEN-CELL CYTOTOXICITY FOR CYTOMEGALOVIRUS-TRANSFORMED CELLS. II. INHIBITION BY CYTOMEGALOVIRUS ANTISERUM. (Eng.) Murasko, D. M. (Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa. 17033); Lausch, R. N. *Int. J. Cancer* 16(1):24-32; 1975.

The ability of serum from LSH inbred hamsters immunized repeatedly with cytomegalovirus (CMV) to block spleen-cell cytotoxicity for CMV-infected and CMV-transformed cells was studied. This inhibition was observed regardless of whether spleen cells were obtained from hamsters sensitized to the virus or to isografts of the transformed cells (designated Cx-90-3B, T-2). Such serum did not significantly block effector cell response against transformed cells expressing herpes simplex virus or simian virus 40-associated membrane antigens. The blocking activity could be absorbed out with Cx-90-3B, T-2 cells, but not by untransformed hamster embryo fibroblasts. Cx-90-3B, T-2 target cells treated with serum, and then washed, remained resistant to effector cell attack. On the other hand, if serum-treated attacker cells were washed, their cytotoxic activity was not significantly impaired. These results suggest that the blocking factor in the serum is antibody-directed against cytomegalovirus-related membrane antigen. This conclusion is supported by the finding that the serum contained antibody specifically reactive with the transformed cell surface in isotopic antiglobulin tests.

- 5011 LYMPHOPROLIFERATIVE DISEASE IN A COTTON-TOP MARMOSET AFTER INOCULATION WITH INFECTIOUS MONONUCLEOSIS-DERIVED EPSTEIN-BARR VIRUS. (Eng.) Werner, J. (Virusabteilung im Robert Koch-Institut des Bundesgesundheitsamtes, Nordufer 20, 1 Berlin 65, Germany); Wolf, H.; Apodaca, J.; Zur Hausen, H. *Int. J. Cancer* 15(6):1000-1008; 1975.

The responses of cotton-top marmosets to inoculation with either active Epstein-Barr virus (EBV) or virus which had been exposed to EBV-specific antibody-containing human serum are described. Injection of con-

centrated EBV derived from cells of the Kaplan line of infectious mononucleosis (IM) origin resulted in malignant lymphoproliferation in one of three cotton-top marmosets six wk after inoculation. Two additional animals receiving the same isolate after incubation with an antibody-containing human serum did not develop tumors. Inoculation of concentrated virus derived from the P3HR-1 line of Burkitt origin did not lead to lymphoproliferation in five marmosets. Three of these received non-neutralized, and two received neutralized P3HR-1 virus. The tumor obtained with the Kaplan isolate revealed characteristics of a lymphosarcoma. It contained EBV-specific DNA. In addition, EBV-synthesizing lymphoblastoid lines were established from a tumorous lymph node, as well as from the spleen of the diseased marmoset. Virus recovered from these lines transformed lymphocytes derived from spleens of healthy marmosets. The tumor-bearing animal developed low levels of anti-viral capsid antigen antibodies during the course of tumor growth. These data demonstrate the oncogenic potential of EBV directly derived from cells of IM origin.

- 5012 EPSTEIN-BARR VIRUS ASSOCIATED WITH EPISODES OF RECURRENT TONSILLITIS. (Eng.) Veltri, R. W. (West Virginia Univ. Medical Center, Morgantown, W. Va.); Sprinkle, P. M.; McClung, J. E. *Arch. Otolaryngol.* 101(9):552-556; 1975.

Twenty-six patients (age range 3-24 yr) with recurrent tonsillitis were monitored microbiologically and serologically after an acute episode of illness. The Henle indirect fluorescent antibody technique was employed to assay anti-early antigen titers of Epstein-Barr virus (EBV). Erythematous hyperplastic tonsils were present in 73% of the patients; 60% had exudate on their tonsils and had at least three tonsillitis attacks per year. Of the 72 serum samples taken, 54 samples from 17 of the 26 (65%) patients were positive for antibodies to early antigen and exhibited a substantial seroconversion to the early antigen of EBV-infected lymphoblastoid cells (P3HR-1 Burkitt lymphoma cell line). No other viral or bacterial pathogen could be implicated from the microbiological data. The authors demonstrate that a high incidence of tonsillitis is associated with the EBV implicating the tonsils as a primary focus for EBV infection. In addition, they suggest that the propensity of the virus for the tonsils may be due to their rich source of B cells. This study confirms the value of monitoring early antigen titers to confirm the nature of infection.

- 5013 NASOPHARYNGEAL CARCINOMA. X. PRESENCE OF EPSTEIN-BARR GENOMES IN SEPARATED EPITHELIAL CELLS OF TUMOURS IN PATIENTS FROM SINGAPORE, TUNISIA AND KENYA. (Eng.) Desgranges, C. (International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69008 Lyons, France); Wolf, H.; de-The, G.; Shanmugaratnam, K.; Cammoun, N.; Ellouz, R.; Klein, G.; Lennert, K.; Munoz, N.; zur Hausen, H. *Int. J. Cancer* 16(1):7-15; 1975.

Nasopharyngeal carcinoma (NPC) biopsies from Singapore, Tunisia and Kenya were compared, before and

after separation of epithelial and lymphoid cells, for their Epstein-Barr virus (EBV)-DNA content, using the cellular DNA-EBC complementary RNA hybridization test. In all instances where separation of the two cell types was achieved, epithelial tumor cells showed a higher EBV-DNA content than lymphoid cells or tumor before cell separation. Thus, EBV-DNA is mostly limited to epithelial cells. No significant difference was observed between NPC tumors originating from various geographical areas.

- 5014 5'-NUCLEOTIDE PHOSPHODIESTERASE ISOENZYME IN PATIENTS WITH HEPATITIS B INFECTION. (Eng.) Tsou, K. C. (Hosp. Univ. Pennsylvania, 3400 Spruce St., Philadelphia, Pa. 19104); McCoy, M. G.; Lo, K. W.; London, W. T. *Cancer Res.* 35(9):2361-2364; 1975.

The interrelationships between hepatitis B surface antigen (HBsAg, Australia antigen) and the fast-moving 5'-nucleotide phosphodiesterase Band V isoenzyme (5'-NPDase-V) were studied to test the hypothesis that hepatitis B infection is related to hepatoma etiology. Sera from 58 patients with viral hepatitis were tested for 5'-NPDase-V and HBsAg. The isoenzyme was found in 34 of 37 patients who were also positive for HBsAg but in only 4 of 21 hepatitis patients who were HBsAg negative. Five patients convalescing from hepatitis were negative for both HBsAg and the isoenzyme. Preparative gel electrophoresis showed that these two markers were different proteins. Of 34 hepatoma patients, 29 were positive for 5'-NPDase-V. Only one isoenzyme-positive patient was positive for HBsAg by counter-immunoelectrophoresis. However, of 16 isoenzyme-positive hepatoma patients available for radioimmunoassay, eight were HBsAg positive (50%). None of 21 hepatoma samples tested for antibody to HBsAg was positive. Of 21 "normal" carriers of HBsAg and ten carriers with Down's syndrome, four persons were detected with the isoenzyme. The results suggest that HBsAg and 5'-NPDase-V in the presence of liver damage are associated and thus provide a new marker enzyme between hepatitis B infection and hepatoma.

- 5015 POSSIBLE PEPTIDE CHAIN TERMINATION MUTANTS IN THYMIDINE KINASE GENE OF A MAMMALIAN VIRUS, HERPES SIMPLEX VIRUS. (Eng.) Summers, W. P. (Yale Univ. Sch. Medicine, 333 Cedar St., New Haven, Conn. 06510); Wagner, M.; Summers, W. C. *Proc. Natl. Acad. Sci. USA* 72(10):4081-4084; 1975.

Mutations in the viral gene coding for the thymidine Kinase (ATP:thymidine 5'-phosphotransferase) induced by herpes simplex virus were obtained by selection of virus resistant to bromodeoxyuridine when grown in thymidine-kinase-deficient LMTK⁻ mouse cells. Proteins labeled after infection of Vero (monkey) cells with herpes simplex virus were analyzed by gel electrophoresis, and one protein of about 40,000 daltons was consistently altered in a number of thymidine-kinase-deficient mutants. Many viral mutants lacked this peptide, and one class of these mutants induced the synthesis of new shorter peptides. Revertant virus could be selected which simultaneously regained the ability to induce thymidine kinase activity.

ity, regained the intact thymidine kinase peptide, and lost the ability to synthesize the shorter peptide fragment. These mutants comprise a class of animal virus mutants that have the properties expected of peptide chain termination mutants.

- 5016 VIRUS REPLICATION AND CELL MODIFICATIONS IN ORGAN CULTURES OF TUMOR TISSUE FROM CHICKENS WITH MAREK'S DISEASE. (Eng.) Coudert, F. (Institut National de la Recherche Agronomique, Station de Pathologic Aviaire, Centre de Recherches de Tours, 37 380 Monnaie, France); Cauchy, L. *J. Natl. Cancer Inst.* 55(1):47-51; 1975.

Explants of testicular and ovarian lymphomas from chickens infected with Marek's disease (MD) virus were examined by electron microscopy at various times after initiation of cultures. Nonenveloped herpes-type virions were observed in explants after 18 days of culture. Infected cells were numerous between days 30 and 63 of culture; most infected cells were morphologically similar to lymphoblastoid cells with vacuoles containing cell debris. Virus replication after day 63 was related to cell lysis. However, a few intact cells without virus were observed around day 100; this suggested that these cells were transformed and nonpermissive. In testicular cultures, virus particles were also seen in cells similar to primitive Sertoli's cells. In contrast to the ovarian and testicular explants, feather-follicle explants contained virus particles only during the first few days in culture. These results unequivocally demonstrate that lymphoid cells of tumors induced by MD virus are sites of virus replication under proper culture conditions. The data also indicate that the affected lymphoid cells can simultaneously be target cells for the infection and neoplastic transformation. Thus, in MD, lymphoid cells undergoing both permissive lytic and nonpermissive infection may appear in the same lymphoma.

- 5017 IN VITRO TRANSFORMATION OF LYMPHOID CELLS BY ABELSON MURINE LEUKEMIA VIRUS. (Eng.) Rosenberg, N. (Cent. Cancer Res., Massachusetts Inst. Technol., Cambridge); Baltimore, D.; Scher, C. D. *Proc. Natl. Acad. Sci. USA* 72(5):1932-1936; 1975.

Cell cultures prepared from fetal murine liver were infected by Abelson murine leukemia virus (A-MuLV) in order to study the effect of a leukemia virus on hematopoietic cells. Cell cultures were prepared from shredded livers of embryos from 12- to 16-day pregnant Swiss or Balb/c mice. About 7.5×10^5 nucleated cells were plated in 30-mm petri dishes and maintained at 37 C. A-MuLV was prepared from a cloned NIH/3T3 nonproducer cell line, and cell cultures were infected with 0.5 ml of A-MuLV stock. Immunoglobulin on the surface of transformed cells was detected by direct immunofluorescent staining. Adult Balb/c mice were injected ip with 0.5 ml of Balb/c lymphoid cells transformed by A-MuLV and passaged with 2-mercaptoethanol. Cells transformed by A-MuLV resembled lymphoblasts and resembled the ascites form of tumors induced *in vivo* by A-MuLV. Cellular transformation was enhanced *in vitro* by

mercaptoethanol. No transformation occurred in mock-infected mercaptoethanol-treated cultures. In 50% of the A-MuLV infected untreated fetal liver cells, a second, nonlymphoid cell was noted 3-4 wk. after infection. Sixty to ninety percent of A-MuLV-transformed lymphoid cells had immunoglobulin. Mice injected with isolated lymphoid cells all developed solid tumors and ascites in 24 days. The results demonstrate that A-MuLV causes lymphoid cells to undergo malignant transformation *in vitro*. Because of this, the authors suggest that it may induce leukemia by directly affecting cellular growth control.

- 5018 PERTURBATIONS OF ERYTHROBLASTIC KINETICS IN THE SPLEEN OF MICE INFECTED BY THE FRIEND VIRUS. (Eng.) Smadja-Joffe, F. (Inst. de Cancerologie et d'Immunogenetique, Villejuif, France); Jasmin, C.; Tambourin, P. E.; Malaise, E. P. *Cell Cycle in Malign. Immun., Proc. Annu. Hanford Biol. Symp., 13th.* Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 277-292.

The kinetic parameters of the polycythemic variety of Friend leukemia were studied in female DBA/2 mice inoculated with the virus (0.2 ml containing 50 spleen dose 50%, iv). Almost all leukemic cells (hyperbasophilic proerythroblasts) were in active stages of the cell cycle (mean duration, 7.6 hr). This intense and massive proliferation was unaffected even during the hours preceding death. The multiplication of leukemic cells resulted in three different phenomena: a very small fraction (1/20) of the proliferation accounted for the growth of the spleen and the progressive invasion of the liver and the blood; 1/3 of leukemic cells differentiated into short-lived RBC; and 2/3 disappeared apparently owing to massive cellular death. From these results it can be concluded that Friend leukemia is a proliferative disease, and that the cumulative model proposed to explain the poor transplantability of Friend cells cannot be accepted.

- 5019 SYNTHESIS OF ERYTHROCYTE-SPECIFIC PROTEINS IN CULTURED FRIEND LEUKEMIA CELLS. (Eng.) Kabat, D. (Univ. Oregon Health Sciences Center Portland, Oreg. 97201); Sherton, C. C.; Evans, L. H.; Bigley, R.; Koler, R. D. *Cell* 5(3):331-338; 1975.

Synthesis of specific proteins in two permanent lines of Friend virus-induced erythroleukemia cells (Friend line 745 and Ostertag line FSD-1, both derived from DBA/2 mice) was studied. By 96 hr after treatment with 1-2% dimethyl sulfoxide (Me_2SO), up to 25% of the protein synthesized by both these cultures is hemoglobin. At that time, hemoglobin constitutes up to 10% of the soluble cellular protein. Both lines synthesize heme and globin coordinately, and α and β globin chains in a nearly balanced 1:1 ratio. However, the ratio of β^{Major} : β^{Minor} chains synthesized by these induced Friend leukemia (FL) cells is approximately nine in the FSD-1 line and 1.3 in the Friend Clone 745 line, whereas it is four in normal adult DBA/2 mouse RBC. Carbonic anhydrase activity/mg protein is three times higher in induced than in control cultures. 2,3-Diphosphoglyceric acid is not found in induced FL cells. Induced and control

FL cells agglutinate strongly and equally with *Phaseolus vulgaris* phytohemagglutinin. The developmental process in these cultured leukemia cells appears to be an aberrant erythropoiesis.

5020 A KINETIC ESTIMATION OF BASE SEQUENCE COMPLEXITY OF NUCLEAR POLY(A)-CONTAINING RNA IN MOUSE FRIEND CELLS. (Eng.) Getz, M. J. (Beatson Inst. Cancer Res., Glasgow, Scotland); Birnie, G. D.; Young, B. D.; MacPhail, E.; Paul, J. *Cell* 4(2):121-129; 1975.

Complementary DNA was transcribed by viral reverse transcriptase (prepared from avian myeloblastosis virus) from poly(A)-containing nuclear RNA prepared from growing mouse Friend cells. Template RNA was incubated for two hours in a reaction mixture containing 200 µg/ml reverse transcriptase. The complementary DNA was isolated by chromatography on Sephadex G-50 after the addition of 50 µg *Escherichia coli* DNA as carrier, fractionated on sucrose gradients, and recovered by neutralization and precipitation with ethanol. Mixtures of mouse embryo DNA and complementary DNA (0.25 ng) were heat denatured, annealed at 60 C and fractionated on hydroxyapatite columns. Single-stranded and double-stranded DNAs were eluted with 0.16 M and 0.4 M phosphate buffer, respectively. RNA was hybridized with complementary DNA, and the proportion of complementary DNA in the hybrid was determined by adding 0.1 ml S1 nuclease and measuring the proportion of radioactivity rendered and soluble by incubation for two hours. The complementary DNA transcribed from poly(A)-containing nuclear RNA had a molecular weight of 1.1×10^5 daltons, corresponding to a single-strand chain length of approximately 400 nucleotides. The synthesis of complementary DNA from nuclear poly(A)-containing RNA was greater than 98% dependent on the inclusion of oligo(dT) in the reaction mixture indicating that this complementary DNA represents copies of 400 nucleotide sequences located immediately adjacent to poly(A) tracts in nuclear RNA. The annealing experiments demonstrated that 80% of the complementary DNA was transcribed from RNA sequences that were transcribed from nonrepetitive DNA in the mouse genome. The kinetics of hybridization of complementary DNA to template RNA indicated that nuclear poly(A)-containing RNA consists of at least two abundance classes, the more complex of which is transcribed from approximately 3% of the genome. The base sequence complexity of the poly(A)-containing nuclear RNA was estimated to be 2×10^{10} to 3×10^{10} daltons. At least five times more unique DNA sequences appear to be represented in nuclear poly(A)-containing RNA than in polysomal poly(A)-containing RNA even though these RNAs are of similar size. This is in agreement with previously published suggestions that there is qualitative control of gene expression at a post-transcriptional level.

5021 EFFICIENT RELEASE OF MURINE XENOTROPIC ONCORNAVIRUS AFTER MURINE LEUKEMIA VIRUS INFECTION OF MOUSE CELLS. (Eng.) Fischinger, P. J. (Natl. Cancer Inst., Bethesda, Md.); Nomura, S. *Virology* 65(1):304-307; 1975.

The theory that murine oncornavirus stocks could become contaminated with a virus group of a dif-

ferent host range and neutralization properties, even if previously passaged murine sarcoma virus or murine leukemia virus was composed of only one virus group, was examined. The virus progeny from a single cycle of Moloney murine leukemia virus infection of either normal or several types of murine sarcoma virus-transformed outbred or inbred mouse cells was investigated. The infecting Moloney murine leukemia virus derived from chronically infected 3T3FL cells was free of detectable xenotropic virus, but its ecotropic content was more than 10^6 focus-inducing U/ml in mouse S+L- cells. No cell line released free murine xenotropic oncornavirus spontaneously. Chemical induction with iododeoxyuridine released low amounts of murine xenotropic oncornavirus from normal BALB/c 3T3 cells and significantly more from K-murine sarcoma virus-transformed nonproducer cells. None of the outbred lines released any detectable murine xenotropic oncornavirus after chemical induction. Infection with Moloney murine leukemia virus resulted in the release of murine xenotropic oncornavirus from normal 3T3FL cells and wild mouse SC-1 cells but not from the revertant SR derived from S+L- 3T3FL cells. BALB/c 3T3 cells yielded low titers of murine xenotropic virus on occasion after ecotropic virus infection. After murine leukemia virus infection, K-BALB cells produced a higher titer of murine xenotropic virus than seen by any other method of induction (more than ten-fold greater than after iododeoxyuridine induction). A high titer of murine xenotropic virus (10^3 focus-inducing U/ml) was produced by S+L- mouse cells after murine leukemia virus infection; these same cells were not all inducible for murine xenotropic virus by iododeoxyuridine. This virus was also completely neutralized by antisera from normal old NZB mice that were specific for murine xenotropic virus and that did not neutralize standard ecotropic types of murine leukemia virus. It is concluded that the murine xenotropic virus must have come from within the mouse cell because repeated attempts at infection of 3T3, S+L-, or revertant mouse cells with more than 10^5 focus-inducing U of murine xenotropic virus resulted in an immediate loss of infection and no reappearance despite several blind passages.

5022 TEMPERATURE-SENSITIVE MUTANTS OF MURINE LEUKEMIA VIRUS. V. IMPAIRED LEUKEMOGENIC ACTIVITY *IN VIVO*. (Eng.) Greenberger, J. S. (Natl. Cancer Inst., Bethesda, Md. 20014); Stephenson, J. R.; Aaronson, S. A. *Int. J. Cancer* 15(6):1009-1015; 1975.

The *in vivo* biologic activities of a clonal isolate of the Rauscher strain of murine leukemia virus (R-MLV) and several conditional lethal mutants with impaired replicative functions at the nonpermissive temperature (37-38 C) were investigated. The temperature-sensitive (ts) mutants 19 and 29 are defective in early postpenetration replication steps, and ts 25 and ts 26 are defective in the late stages of replication. Wild type (wt) R-MuLV and the ts mutants were compared in terms of their infectivity in newborn NIH Swiss mice, their leukemogenicity in NIH Swiss mice, and the hematologic and histopathologic changes associated with their infection of suscep-

tible animals. Within two wk, the spleen cells from 100% of the newborn mice infected with wt R-MuLV contained detectable infectious virus; greater in the spleens of the R-MuLV-infected mice than in the spleens of mice infected with C58-MuLV, a known oncogenic type-C virus. Spleen cells from the mice inoculated with the four ts mutants showed no detectable virus production at the permissive temperature (31°C) up to 30 wk after inoculation. The wt R-MuLV induced leukemia within 12 mo in over 90% of the mice inoculated as newborns; the affected animals demonstrated listlessness, pallor, hair loss, massive spleen swelling, visceral blanching, and lymph-node and liver enlargement. C58-MuLV was somewhat less tumorigenic, and the ts mutants of R-MuLV were non-tumorigenic, producing no clinical or gross pathological signs of leukemia. Similarly, while wt R-MuLV produced severe anemia and microscopic evidence of lymphoid leukemia in the affected spleens, lymph nodes, and livers, the ts mutants produced no such changes. The results suggest that persistent virus replication is in some way linked to the development of disease and demonstrate that tissue culture passage does not necessarily lead to virus attenuation. Type-C viral mutants may be useful in the experimental immunoprevention and therapy of type-C virus-induced disease.

5023 POTENTIATING EFFECT OF IODODEOXYURIDINE ON MuLV REPLICATION IN MOUSE EMBRYO FIBROBLASTS. (Eng.) Niwa, O. (Stanford Univ. Sch. Medicine, Stanford, Calif. 94305); Decleve, A.; Kaplan, H. S. *Virology* 67(1):158-167; 1975.

The potentiating effect of 5-iododeoxyuridine (IUdR) on endogenous and exogenous virus replication in C57BL mouse embryo fibroblasts (BL-MEF) was studied. Secondary cultures of BL-MEF and radiation leukemia virus (RadLV)-infected cells (BL-5) were treated with IUdR (1-100 µg/ml) for 24 hr, and both cell growth and virus titer were monitored thereafter. In some experiments, thymidine (TdR) was added to the cultures in the same concentration as the added IUdR. In other experiments, the effects of IUdR on murine leukemia virus (MuLV)-infected rat NRK cells and on Gross-AKR MuLV (GLV)-infected BL-MEF were determined. The data revealed a 2- to 3-fold increase in the cellular susceptibility to MuLV infection as determined by measuring the number of immunofluorescence-positive or plaque-forming cells in IUdR-pretreated cells infected by RadLV or GLV, without a concomitant change in viral replication kinetics or in the yield of infectious viruses. Host-range studies of the progeny virus from the IUdR-pretreated RadLV- or GLV-infected cells suggested that the progeny virus retained the original characteristics of the input exogenous virus. UV irradiation had no potentiating effect on virus replication in BL-MEF cells infected with RadLV. No evidence was obtained to support the hypothesis that IUdR potentiation results from the induction of endogenous virus followed by complementation or recombination between endogenous and exogenous virus. Instead, the responsible mechanism appears to involve IUdR-induced DNA strand breakage, repair, and enhanced recombinational integration of the exogenous viral genome into cellular DNA.

5024 REQUIREMENT FOR CELLULAR PROTEIN SYNTHESIS IN REVERSAL OF ETHIDIUM-BROMIDE-INDUCED INHIBITION OF CELL TRANSFORMATION BY MURINE SARCOMA VIRUS. (Eng.) Roa, R. C. (St. Louis Univ. Sch. Medicine, St. Louis, Mo. 63104); Bose*, S. K. *Proc. Natl. Acad. Sci. U.S.A.* 72(11):4337-4340; 1975.

The ability of ethidium bromide (EtdBr)-treated Balb 3T3 mouse cell cultures to regain the capacity for successful infection after incubation in EtdBr-free growth medium is described. Infectivity by the Harvey strain of murine sarcoma virus (H-MSV) was determined by the focus assay with 25 µg/ml of polycation incorporated into the virus inoculum. The number of foci developing in the infected cultures returned to normal when the infection was delayed for various lengths of time after EtdBr treatment of cultures was terminated; full recovery occurred when cultures were incubated for six hours in drug-free medium. The foci forming on cells infected immediately after 18 hr exposure to 1 µg/ml of EtdBr was 24% of the control. The extent of inhibition was virus dose-dependent. Brief exposure (six hours) of cultured fibroblasts to protein synthesis inhibitors at the time of infection did not lead to suppression of virus replication; cultures exposed to cycloheximide (10 µg/ml), chloramphenicol (1 mg/ml) or actinomycin D (0.01 µg/ml) showed no inhibition of the virus-induced focus formation. Caffeine (2 mM) or acriflavin (50 µg/ml) had no effect on focus development after infection with MSV. In contrast, cordycepin pretreatment (10 µg/ml), which may act at the level of polyadenylation of messenger RNA or DNA synthesis, completely inhibited the recovery process. The authors conclude that the recovery of EtdBr-treated cultures requires the synthesis of cellular proteins. This may have some important role in the establishment of RNA tumor virus infection.

5025 STUDIES ON A TRANSPLANTABLE MURINE RHABDOMYOSARCOMA. (Eng.) Perk, K. (Natl. Cancer Inst., Bethesda, Md. 20014); Gazdar, A. F.; Russell, E. R. *J. Natl. Cancer Inst.* 54(5):1207-1213; 1975.

The development of rhabdomyosarcomas in mice inoculated with Moloney strain of murine sarcoma virus (M-MuSV) was studied. Representative samples of transplanted tumors, various organs, and cell cultures were fixed in chrome osmium and studied electron microscopically. The R2 cell line was started from the 13th tumor transplant passage, and tumor concentrates were subjected to infectivity and complement fixation tests. Cell free preparations derived from two bat tumors, initially induced by mouse-derived MuSV, were tested for oncogenicity in ten newborn BALB/c mice. The animals were inoculated im-sc with 0.05 ml cell-free viral concentrate. After 8-10 mo, 80% of these mice developed progressively growing tumors resulting in death. At death, tumors were extremely large and mainly at the site of inoculation (inguinal area). Histologically, the tumor was predominantly composed of large elongated cells with central nuclei and acidophilic tendencies. Electron microscopy revealed thick and thin myofilaments and myofibrils;

all four initial tumors had numerous cisternal A particles and frequent virus budding, while no C type virus was seen. The primary mouse tumor "induced" by the bat-derived material was consistently transplantable in normal newborn and 4 to 6-wk-old BALB/c mice for 50 generations. Tumors were also transplantable for several generations in DBA/2, NZB, and (NZB x NZW) F_1 hybrid mice, but not in C3H or C57BL/6 mice. Inoculation of 10^6 R2 cells into weanling BALB/c mice resulted in a 100% tumor incidence, with a latent period of less than ten days. However, mice inoculated with concentrates of the R2 line remained healthy. While the relationship between the bat-passaged material and the induction of the mouse tumors was obscure, the appearance of the extremely rare spontaneous rhabdomyosarcoma at the inoculation site suggests a causal relationship.

5026 NATURAL ANTIBODIES DIRECTED AGAINST MURINE LYMPHOSARCOMA CELLS. (Eng.) Pierotti,

M. A. (Div. of Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, Milan 20133, Italy); Colnaghi, M. I. *J. Natl. Cancer Inst.* 55(4):945-949; 1975.

Natural antibodies reacting in a test of complement-dependent cytotoxicity with untreated murine lymphosarcoma cells of thymic origin were found in murine sera. Normal thymus cells were unaffected and unable to absorb the serum activity. The natural antibodies were IgM-like and stable at 56 C. They were not uniformly distributed in the studied strains, and high (C3H/He and C3Hf), intermediate (AKR and CBA/J), and low level strains (BALB/c, DBA/2, C57BL, and C57BL/6J) were found. Hybrids between a high (C3Hf) and a low level strain (C57BL) had the same response as the parental C3Hf mice. An inverse relationship was demonstrated between cytotoxicity of, and susceptibility to, serum of lymphoma cells in a given strain, which suggested an immunologic modulation. Embryonic cells absorbed the cytotoxic activity of the normal serum.

5027 ANALYSIS OF HOST RANGE OF NONTRANSFORMING POLYOMA VIRUS MUTANTS. (Eng.) Goldman,

E. (Harvard Medical Sch., Boston, Mass. 02115); Benjamin, T. L. *Virology* 66(2):372-384; 1975.

The nontransforming polyoma virus mutant, NG-18, was shown to grow in a variety of other cell types besides polyoma-transformed cells. Among cells found to be substantially permissive for the growth of NG-18 are: phenotypic revertants of polyoma-transformed 3T3 cells, C-type RNA virus transformed and/or producing 3T3 cells, 3T3 cells that become transformed upon infection with leukemia virus, primary baby mouse kidney epithelial cells, and primary mouse embryo fibroblasts. Among cells found to be poor hosts for the growth of NG-18 are: several 3T3 cell lines, SV40-transformed 3T3 cells, spontaneously transformed 3T3 cells, radiation- and chemical carcinogen-transformed 3T3 cells, and late passage mouse embryo fibroblasts. Similar results were obtained using three other independently isolated host range mutants of the same type as NG-18. The permissive state thus does not require a cell-

associated polyoma genome as the basis for complementation of growth for this class of host range mutant. In addition, the results demonstrate that cells can be permissive for the growth of such non-transforming virus mutants without themselves possessing properties commonly associated with transformation such as: loss of density-dependent inhibition of growth, low serum requirement for growth, loss of anchorage dependence of growth, and lectin agglutinability. These findings are discussed in reference to possible mechanisms of action of the NG-18 gene in productive infection and transformation.

5028 TEMPERATURE-SENSITIVE GROWTH OF CELLS TRANSFORMED BY *ts-a* MUTANT OF POLYOMA

VIRUS. (Eng.) Kimura, G. (Tottori Univ. Sch. Med., Yonago 683, Japan). *Nature* 253(5493):639-641; 1975.

To determine whether the temperature-sensitive (*ts-a*) gene of polyoma virus affects the growth properties of cells transformed by it, seven independent 3Y1 lines transformed by the *ts-a* mutant at the permissive temperature as well as three 3Y1 lines transformed by wild type (WT) virus were examined for their ability to grow in low (2%) and high (10%) serum medium at 33 and 40 C, the permissive and nonpermissive temperatures for the productive cycle of this mutant. The growth of untransformed and WT-transformed 3Y1 cells was reduced at both temperatures in 2% serum as compared with 10% serum, the reduction being greater in the untransformed cells. In four of the seven *ts-a*-3Y1 lines, growth in 2% serum was less at 40 C than at 33 C, and two lines showed less growth in 10% serum at 40 C as compared with 33 C. Three *ts-a*-3Y1 lines showed little or no temperature-sensitivity for growth under these conditions. When *ts-a*-3Y1 cells grown in 2% serum were shifted from 40 to 33 C and from 33 to 40 C, resumption and slowing down, respectively, of growth occurred within 24 hr. None of six *ts-a*-3Y1 lines produced infectious virus on fusion with BALB/3T3 cells, although when the cocultivation was carried out in the presence of UV-inactivated Sendai virus, four of the *ts-a*-3Y1 lines produced a relatively large amount of virus. The virus rescued from each transformed line was identified as the originally transforming *ts-a*. These data suggest that the transformed lines studied were actually transformed by the virus strains in question. It is suggested that the *ts-a* gene of polyoma virus controls at least one aspect of the maintenance of the transformed state in certain transformed cells, i.e., the ability of transformed cells to grow in low serum medium.

5029 THE INFLUENCE OF PINEALECTOMY AND OF PINEALECTOMY COMBINED WITH THYMECTOMY ON THE ONCOGENESIS CAUSED BY POLYOMA VIRUS IN RATS. (Eng.) Wrba, H. (Inst. Cancer Res., Univ. Vienna, Vienna, Austria); Lapin, V.; Dostal, V. *Oestern. Onkol.* 2(2/3):37-39; 1975.

The oncogenic effect of polyoma virus was studied

in 14 neonatally pinealectomized Wistar rats, on 26 rats neonatally thymectomized, and on ten neonatally pinealectomized rats that were simultaneously thymectomized. The inoculation of polyoma virus suspension (1 ml containing 10 TCID₅₀, sc) to the neonatal pinealectomized rats did not provoke a growth of neoplasia. However, if the pinealectomy was combined with neonatal thymectomy, renal tumors occurred in a rate of 50% of animals. An incidence of renal tumors was observed also in 57.6% of thymectomized rats, but not in 21 non-operated controls.

5030 ROUS SARCOMA VIRUS ACTIVATES EMBRYONIC GLOBIN GENES IN CHICKEN FIBROBLASTS. (Eng.) Groudine, M. (Dept. Biochemical Sciences, Princeton Univ., Princeton, N.J. 08540); Weintraub, H. *Proc. Natl. Acad. Sci. USA* 72(11):4464-4468; 1975.

To determine whether a specific cellular gene, the globin gene, becomes activated after Rous sarcoma virus (RSV) transformation, globin complementary DNA (cDNA) made against globin messenger RNA (mRNA) from adult chicken reticulocytes was annealed with the total RNA from RSV-infected and uninfected chick embryo fibroblasts. The globin cDNA failed to hybridize to the total RNA extracted from uninfected fibroblasts, but RNA complementary to globin cDNA was detectable in amounts of 100-500 copies per cell in RSV-infected fibroblasts. No globin mRNA sequences were detectable in purified RSV RNA. When the globin cDNA probe was reacted with total RNA from fibroblasts infected with a transformation defective (td) RSV, no hybridization was detected, even though the mutant replicated and produced normal numbers of virus particles. In further experiments, chick embryonic RBC RNA was added to a hybridization mixture containing RNA from RSV-transformed fibroblasts and the cDNA probe. Only 71% of the probe was saturated, indicating that the globin sequences that are unique to the adult were not activated during RSV transformation of the chick fibroblasts. Several embryonic globin mRNAs may have been activated. The hybrids formed between the RNA from RSV-infected fibroblasts and the globin cDNA probe were stable. The data suggest a strict correlation between the presence of the "onc" gene (the viral gene which controls the expression of the phenotypic changes associated with RSV transformation), host cell transformation, and the activation of embryonic globin gene transcription.

5031 INHIBITION OF PROTEASE ACTIVITY IN CULTURES OF ROUS SARCOMA VIRUS-TRANSFORMED CELLS: EFFECT ON THE TRANSFORMED PHENOTYPE. (Eng.) Weber, M. J. (Dept. Microbiology, Univ. Illinois, Urbana, Ill. 61801). *Cell* 5(3):253-261; 1975.

The role of proteolytic activity in the genesis and maintenance of the transformed phenotype was examined by growing cultures of chick embryo fibroblasts transformed by Rous sarcoma virus either in medium containing plasminogen-free serum or in medium to which protease inhibitors were added. Alterations in morphology, adhesiveness, and hexose transport were used as markers for the transformed state. Addition

of the trypsin inhibitors nitrophenyl-p-guanidinobenzoate or Soybean trypsin inhibitor at concentrations (5 and 2.5 µg/ml, resp.) which inhibited transformation-associated fibrinolysis restored adhesiveness and morphology to near normal, but did not affect the rate of hexose transport. Growth of Rous-infected cells in plasminogen-free medium blocked the appearance of morphological and adhesive alterations, but allowed the rate of hexose transport to increase to the transformed level. It was thus possible to separate the appearance of transformation-specific changes in morphology and adhesiveness (which apparently require fibrinolytic activity) from the increased rate of hexose transport (which is independent of fibrinolytic activity). Another trypsin inhibitor tosyl-lysyl-chloromethyl ketone (50 µg/ml), although it did not inhibit fibrinolysis, was very effective at restoring adhesiveness and morphology as well as hexose transport to normal. This raises the possibility that yet another protease is involved in the genesis of the transformed phenotype, separate from--and perhaps prior to--plasmin and plasminogen activator.

5032 FIBRIN OVERLAY METHODS FOR THE DETECTION OF SINGLE TRANSFORMED CELLS AND COLONIES OF TRANSFORMED CELLS. (Eng.) Jones, P. (Childrens Hosp. Los Angeles, 4650 Sunset Blvd., Los Angeles, Calif. 90027); Benedict, W.; Strickland, S.; Reich, E. *Cell* 5(3):323-329; 1975.

Fibrin overlay methods are described which can detect the plasminogen activator produced by single transformed cells or small colonies of transformed cells. These methods were applied to malignant cells derived from humans, mice, hamsters, rats, and chicks. Plasminogen-dependent lysis was observed. Transformation of chicken cells by Rous sarcoma virus was detected four days after infection. The number of lysis zones produced was proportional to the virus inoculum and was identical to the number of morphologically determined foci. Transformed mouse and chicken cells were detected at the single cell level and the number of lysis zones produced was dependent on the number of cells present, the time of incubation, and the concentration of plasminogen. It is suggested that these methods may also have application in model systems for scoring transformation by chemicals.

5033 ASSIGNMENT OF GENE(S) FOR CELL TRANSFORMATION TO HUMAN CHROMOSOME 7 CARRYING THE SIMIAN VIRUS 40 GENOME. (Eng.) Croce, C. M. (Wistar Inst. Anat. Biol., Philadelphia, Pa.); Koprowski, H. *Proc. Natl. Acad. Sci. USA* 72(5):1658-1660, 1975.

Somatic cell hybrids between two different simian virus 40 (SV40)-transformed, hypoxanthine phosphoribosyltransferase-deficient human cell lines (skin fibroblasts from a Lesch-Nyhan syndrome patient, and fibroblasts from normal buccal mucosa) and peritoneal macrophages from two mouse strains (C57BL/6 and Balb/c) were studied for the expression of the transformed phenotype, expression of SV40 tumor T-antigen, and presence of human chromosomes. The clones were obtained in hypoxanthine-aminopterin-thymidine selective medium. Giemsa banding staining

was used for karyological analysis, and SV40 antigen was detected by direct immunofluorescence. Criteria for expression of transformed phenotype were lack of density-dependant cell growth inhibition, high saturation density, and colony formation in soft agar. All the hybrid cell clones contained the human chromosome 7 and were SV40 T-antigen positive. No hybrid cell clones studied displayed the density-dependant inhibition of cell growth characteristic of normal cells; all clones had a high saturation density and gave origin to cell colonies when plated in soft agar. Since the expression of the transformed phenotype was always associated with the presence of the human chromosome 7, which carries the SV40 genome, it is concluded that this chromosome contains gene(s) [*Tr* gene(s)] coding for "transforming factor(s)".

5034 SIMIAN VIRUS 40 DNA REPLICATION, TRANSCRIPTION, AND ANTIGEN INDUCTION DURING INFECTION WITH TWO ADENOVIRUS 2-SV40 HYBRIDS THAT CONTAIN THE ENTIRE SV40 GENOME. (Eng.) Siegel, S. E. (Los Angeles Children's Hosp., Los Angeles, Calif. 90027); Patch, C. T.; Lewis, A. M., Jr.; Levine, A. S. *J. Virol.* 16(1):43-52; 1975.

Two stable variants of the adenovirus 1 (Ad2)-simian virus 40 (SV40) hybrid population Ad²⁺ were studied in the BSC-1 and Vero lines of African Green monkey kidney cells, in order to determine the extent of nonhybrid SV40 replication and its pattern of transcription. The variants were Ad²⁺HEY (high-efficiency yielder) and Ad²⁺LEY (low-efficiency yielder). Hybridization-competition experiments indicated that both early and late SV40 RNA was transcribed efficiently in Ad²⁺HEY-infected Vero cells, but only early SV40 RNA was transcribed efficiently in Ad²⁺LEY-infected cells. Ad²⁺HEY induced SV40 U, T, and V antigens during lytic infection of African Green monkey kidney cells, whereas Ad²⁺LEY induced only SV40 U and T antigens. It is concluded that these variations in the behavior of Ad²⁺HEY and Ad²⁺LEY regarding expression of SV40 functions probably reflect differences in the rate of SV40 excision from the hybrid genomes.

5035 SIMIAN VIRUS 40 GENE A FUNCTION AND MAINTENANCE OF TRANSFORMATION. (Eng.) Osborn, M. (Cold Spring Harbor Lab., N.Y.); Weber, K. *J. Virol.* 15(3):636-644; 1975.

Temperature sensitive mutants of simian virus 40 (SV40) were used to isolate transformants of rat embryo cells. Cells from CDF albino inbred (Charles River) rats were infected at low multiplicity (~1 or less) with either wild-type SV40 or the mutant strains tsA7 or tsA28. Transformants were isolated, cloned, and examined for differences in growth properties, morphology, and expression of T-antigen at 33 and 41 C. To measure growth rate, cells were seeded in 10% fetal calf serum at 10⁵ cells/dish and allowed to attach at 33 C. After attachment, half of the plates were shifted to 41 C. Growth rates of both wild-type and mutant transformants were equal at 33 C, but the wild-type grew slightly faster at 41 C, while the tsA28 transformant grew slower and seemed limited to 10- to 12-fold lower

density than at 33 C. Similar results were obtained with 1% fetal calf serum. Phase microscopy showed no morphological changes in wild-type transformation with the temperature change, while the mutants became large and flat at 41 C. Size distribution also became abnormal in the mutant transformants. The size distributions of the wild-type transformants at 33 and 41 C and of the tsA transformant were similar. The distributions were normal and peaked at an arbitrary setting of 30, with only 2% of the cells being larger than 85. Four days after the shift to 41 C, however, no real peak in the tsA was seen, and 30% of the population had a size greater than 85. Staining with actin antibody showed the wild-type transformants at both temperatures, and the mutants at 33 C had few thick actin-containing fibers; the mutants at 41 C showed long, thick fibers. Of the wild-type transformants, 98% had T-antigen at both temperatures at all times tested. The mutants were also 98% positive for 7-antigen at 33 C, but at 41 C the percentage decreased with time. It is concluded that wild-type and mutant transformants behave similarly at permissive temperatures, but differently at nonpermissive temperatures; this suggests that in these cells, the A function is involved in maintaining the transformed state.

5036 TRANSFORMATION-INDUCED ALTERATIONS IN FIBROBLAST ADHESION: MASKING BY TRYPSIN TREATMENT. (Eng.) Cassiman, J. J. (Stanford Univ. Sch. Med., Calif.); Bernfield, M. R. *Exp. Cell Res.* 91(1):31-35; 1975.

To determine whether transformed and untransformed fibroblasts differ in intercellular adhesivity, and whether trypsinization modifies this difference, initial rates of cell aggregation were measured. Simian virus 40 (SV40)-transformed cells and nontransformed BALB/c 3T3 and WI38 cells were placed in suspension with trypsin or EDTA. For the adhesion assay, suspensions were diluted to 1 x 10⁵ cells/ml in serum-free growth medium at pH 7.5. Aliquots of 3 ml were added to bacteriologic culture dishes layered with 2 ml of 1.5% noble agar to prevent adherence to the substratum. The decrease in single cells during gyrotatory incubation (74 rpm) was measured; the mean of two counts was taken for each dish, and duplicate dishes were counted for each time point. The initial aggregation rate per min of the transformed WI38 and 3T3 cells harvested by EDTA was significantly greater (12.6 and 12.8, respectively) than that of their untransformed homologues (1.2 and 7.0, respectively). Cells harvested by trypsin aggregated at significantly lower rates (0 and 3.4, respectively, for transformed; 0 and 4.3, respectively, for nontransformed) than those harvested by EDTA. The transformed cells had the same aggregation rate as the nontransformed cells. This was true even when EDTA was present in the trypsin. The difference in rate between EDTA- and trypsin-harvested cells was not affected by the presence of DNase (10 µg/ml) or 2% trypsin soybean inhibitor. There was no difference between harvesting agents in cell viability or in the proportion of cells (about 80%) found in aggregates after 18 hr incubation in medium with fetal calf serum. Elevated cell density (typical of transformed cells) did not alter the aggregation rate of the transformed 3T3

cells, and slightly reduced that of the transformed WI38 cells. It is concluded that SV40 transformation of 3T3 and WI38 cells increases the cell aggregation rate, and that trypsinization masks this increase.

5037 DEMONSTRATION OF INFECTIOUS DNA IN TRANSFORMED CELLS. II. CHARACTERIZATION OF UPTAKE OF SV40-TRANSFORMED MOUSE CELL DNA BY SIMIAN CELLS. (Eng.) Kelly, R. K. (Freshwater Inst., Winnipeg, Manitoba, Canada); Butel, J. S. *Arch. Virol.* 48(4):279-287; 1975.

The initial steps in the DNA-transfer, or transfection, method of virus rescue were characterized using primary green monkey kidney (GMK) cells exposed to Simian virus 40 (SV40)-transformed mouse (SV-3T3) cell DNA in the presence of 1 mg/ml DEAE-dextran. When large amounts (10-50 µg) of high molecular weight DNA (> 10⁷ daltons) were inoculated onto 10⁶ GMK cells, usually less than 1 µg became cell-associated. DNA fragmented to a size of 1 x 10⁶ to 3 x 10⁶ daltons was bound more efficiently by the recipient cells, but generally only 5-10% of the inoculum (representing 1-4 µg) was taken up. Approximately 50% of the cell-associated DNA had penetrated to a DNase-resistant state by the end of the 30 min incubation. The effect of the size of the transformed cell DNA molecule on the recovery of SV40 in transfection experiments was investigated. The trend appeared to be that rescue was more efficient with the larger molecular weight samples.

5038 CONSTRUCTION IN VITRO OF MUTANTS OF SIMIAN VIRUS 40: INSERTION OF A POLY-(dA·dT) SEGMENT AT THE HEMOPHILUS PARAINFLUENZA II RESTRICTION ENDONUCLEASE CLEAVAGE SITE. (Eng.) Carbon, J. (Dept. Biological Sciences, Univ. California, Santa Barbara, Calif. 93106); Shenk, T. E.; Berg, P. *J. Mol. Biol.* 98(1):1-15; 1975.

A biochemical procedure was developed for the construction of covalently closed circular double-stranded DNA containing a short segment of poly-(dA·dT) inserted at a specific site. Circular simian virus 40 (SV40) DNA with a short (about 50 base-pairs) insertion of poly(dA·dT) at the site cleaved by the *Hemophilus parainfluenza* II restriction endonuclease (0.735 map position) was prepared. The insertion interrupted the normal nucleotide sequence and altered the viral phenotype. Circular SV40(I)-DNA was cleaved with the *Hpa*II endonuclease to form unit-length, double-stranded linear molecules; the exposed 5' ends were trimmed back by λ 5'-exonuclease digestion; short extensions of poly(dA) or poly(dT) were added to the exposed 3'-hydroxyl ends with terminal deoxynucleotidyl transferase; an equimolar mixture of the poly(dA) and poly(dT)-ended linear DNAs was denatured and then annealed to reform duplex structures; and the resulting hydrogen-bonded circular molecules were covalently sealed in the presence of DNA polymerase I and DNA ligase. The viral DNA containing the insertion at 0.735 map position was found to be infectious without a helper virus, although plaques produced on monolayers of monkey kidney cells (CV-1P) appeared later and were

much smaller than those produced by wild-type DNA. At least a portion of the inserted poly(dA·dT) sequence was maintained through repeated cycles of viral growth in monkey cells, and could be located in the viral DNA by a modification of standard electron microscopic heteroduplex techniques. The method should be applicable for the preparation of insertion mutants in any infectious circular double-stranded DNA, depending on the availability of endonucleases capable of cleaving the DNA at single unique sites.

5039 PROPERTIES OF THE GENOME IN NORMAL AND SV-40 TRANSFORMED WI-38 HUMAN DIPLOID FIBROBLASTS. III. TURNOVER OF NONHISTONE CHROMOSOMAL PROTEINS AND THEIR PHOSPHATE GROUPS. (Eng.) Krause, M. O. (Dept. Biochem. Univ. Florida, Gainesville); Kleinsmith, L. J.; Stein, G. S. *Life Sci.* 16(7):1047-1058; 1975.

The turnover of nonhistone chromosomal proteins and their phosphate groups was compared in normal and in simian virus 40 (SV40)-transformed WI-38 human diploid fibroblasts. Cells were pulse labeled with tryptophan-³H and ³²P for 30 min and the specific activities of tryptophan-³H and ³²P in the molecular weight classes of nonhistone chromosomal proteins were determined during the first four hours following termination of labeling. While a rapid turnover of high-molecular weight nonhistone polypeptides (142,000-200,000 daltons) is evident after one hour in SV40-transformed cells, the specific activities of these nonhistone chromosomal polypeptides are not significantly decreased in normal cells. In contrast, a rapid turnover of low-molecular weight (30,000-51,000 daltons) nonhistone chromosomal proteins occurs during the first hour in normal WI-38 cells with no corresponding decrease in the specific activities of these proteins in SV-40 transformed cells. There is no apparent net turnover of phosphate groups on nonhistone chromosomal proteins in either normal or SV-40 transformed cells four hours following pulse labeling. Rather, during the first four hours, significant fluctuations are observed in the ³²P specific activities of defined molecular weight fractions. Taken together with previous reports of differences in the composition, synthesis and phosphorylation of nonhistone chromosomal proteins in normal and SV40-transformed human diploid cells, the present results further indicate the complex nature of the alterations in these proteins which accompany viral transformation.

5040 MUTAGENESIS INDUCED BY SIMIAN VIRUS 40 (SV 40). II. INDUCED MUTATIONS TO PURINE-BASE ANALOGUES RESISTANCE IN HUMAN AND CHINESE HAMSTER CELLS. (Rus.) Marshak, M. I. (I. V. Kurchatov Inst. of Atomic Energy, Moscow, U.S.S.R.); Varshaver, N. B.; Shapiro, N. I. *Genetika* 11(2): 92-104; 1975.

The ability of simian virus 40 (SV40) strain 128 to induce mutants resistant to guanazidine in hypotriploid and hypodiploid human cell lines, and mutants resistant to 6-mercaptopurine in Chinese hamster cell lines was studied. The SV40 was found to penetrate into the cells and to induce T-antigen synthesis. In a medium lacking serum growth factor,

the number of colony forming Chinese hamster cells was highest 24 hr after infection. By culturing cells in the medium lacking serum growth factor, a Chinese hamster cell subline was isolated which was found to synthesize T-antigen within 60 days after virus infection, which is regarded as an indirect proof of the incorporation of the virus genome in the cell genome. The increased frequency of mutants resistant to guanazidine (60 µg/ml) and 6-mercapto-purine (15 or 30 µg/ml) was observed between the first and fourth days following infection. The induction of resistant mutants was determined to be highly significant. The resistance of the isolated clones was stable in the course of culturing under nonselective conditions. It is suggested that virus genome incorporation, gene mutations, and chromosome aberrations may have common molecular mechanisms. The mutagenic action of SV40 is apparently not related to the virus DNA synthesis or to virus particle formation. The malignantly transformed phenotype may appear not only as a result of the repression or derepression of certain cell genes, but also as a result of virus-induced mutations in the corresponding genes. After malignant transformation, the virus-induced mutagenesis plays an important role in the progression of the tumor growth since it may involve the accumulation of mutants resistant to antineoplastic drugs.

5041 SYNTHESIS OF SUPERHELICAL SIMIAN VIRUS 40 DEOXYRIBONUCLEIC ACID IN CELL LYSATES.

(Eng.) DePamphilis, M. L. (Stanford Univ. Med. Cent., Calif.); Beard, P.; Berg, P. *J. Biol. Chem.* 250(11): 4340-4347; 1975.

An *in vivo* system, which uses a lysate of simian virus 40 (SV40)-infected monkey cells with intact nuclei, to convert SV40(RI) to the covalently closed superhelical form SV40(I), is described. Replication *in vitro* occurred at 1/3 the *in vivo* rate for 30 min at 30 C. After one hr of incubation, about 54% of the replicating molecules were converted to SV40 (I), 5% to nicked, circular molecules (SV40(II)), 5% to covalently closed dimers; the remainder failed to complete replication, although 75% of the prelabeled daughter strands had been elongated to one-genome length. Density labeling *in vitro* showed that all replicating molecules had participated during DNA synthesis *in vitro*. Velocity and equilibrium sedimentation analysis of pulse-chased and labeled DNA using radioactive and density labels suggested that SV40 DNA synthesis *in vitro* was a continuation of normal ongoing DNA synthesis. Initiation of new rounds of SV40 DNA replication was not detectable. The observations on *in vitro* DNA synthesis suggest that normal chain elongation, termination, and segregation can occur in a cell-free extract.

5042 BIOCHEMICAL PROCEDURE FOR PRODUCTION OF SMALL DELETIONS IN SIMIAN VIRUS 40 DNA.

(Eng.) Carbon, J. (Stanford Univ. Med. Cent., Calif.); Shenk, T. E.; Berg, P. *Proc. Natl. Acad. Sci. USA* 72(4):1392-1396; 1975.

A biochemical procedure for producing small deletions (15-50 base pairs) at any location on simian virus 40

(SV40) DNA is reported. SV40 DNA was extracted from CV-1 cells infected at 0.01 plaque forming units (PFU) per cell. The procedure involves the cleavage of the SV40 (I) closed-circular DNA with either *Hpa*II or *Eco*RI restriction endonuclease to produce a linear structure, followed by λ 5'-exonuclease (10 µg/ml, 0 C, 30 min) digestion to expose a short single-stranded segment at each 3' end of the molecule. The modified DNA is then separated by electrophoresis through 4% agarose. *Hpa*II endonuclease-cleaved SV40 DNA [SV40 (L_{Hpa}II)] yielded plaques on CV-1P monolayers. These plaques from SV40(L_{Hpa}II) DNA treated with λ 5'-exonuclease [SV40(L_{Hpa}IIexo)] were much smaller and appeared later than those produced by the SV40(L_{Hpa}II) DNA. In each case, the DNA was resistant to cleavage by *Hpa*II endonuclease, indicating that the mutant DNA no longer contained an intact *Hpa*II cleavage site. The *Hind*III fragment C, generated from the DNA of each of these mutants, migrated faster on acrylamide gels than did the wild-type fragments, indicating that the mutant fragment was smaller. Mutants *dl* 861 and *dl* 862 lacked 32 and 53 base pairs, respectively. When SV40 DNA, cleaved at the *Eco*RI restriction site, was digested with exonuclease, the specific infectiveness of the DNA dropped to a low value of 2×10^3 PFU/µg. It is concluded that the alteration of the *Eco*RI endonuclease sites affected the B cistron function, but not the A function expression. The proposed model was consistent with the finding that linear molecules with single-stranded 'tails' of 25-30 bases yielded mutants with deletions of about 15-50 base pairs.

5043 COMPETITION RADIOIMMUNOASSAY FOR MASON-PFIZER MONKEY VIRUS: COMPARISON WITH RECENT ISOLATES.

(Eng.) Yeh, J. (Pfizer Inc., Maywood, N.J.); Ahmed, M.; Lyles, J.; Larson, D.; Mayyasi, S. A. *Int. J. Cancer* 15(4):632-639; 1975.

Radioimmunoassay (RIA) was used in the detection of small amounts of Mason-Pfizer monkey virus (M-PMV)-specific antigen in tissue, virus, and cell culture preparations. The major core protein (27,000 daltons, designated p27) of M-PMV was purified by exchange chromatography, the resulting fractions were analyzed by immunodiffusion against anti-M-PMV serum. Immunoreactive fractions were analyzed by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Fractions were analyzed by microimmunodiffusion with antiserum made against sonicated whole virus. Purified p27 protein was iodinated and analyzed by radioimmunoassay. The serum, up to a 500-fold dilution, was able to precipitate the labeled antigen. A serum dilution of 1:2,000 precipitated 60% of the ¹²⁵I-p27. This dilution was chosen for use in competition studies in which p27 was compared with the following: simian viruses X-381 and FTP-1; human viruses AO and J-96; mouse mammary tumor virus (MuMTV); and with the p27 of simian sarcoma virus (SSV-1) and p30 of Rauscher leukemia virus (RLV). FTP-1, X-381 and AO viruses showed similar slopes and plateaued at the same level as M-PMV and its p27, demonstrating that this virus has structural proteins antigenically identical to p27. J-96 virus was similar to M-PMV, although it was not identical. MuMTV, SSV-1, and p30 of RLV showed no antigen similar to M-PMV. RIA can

be used to detect the presence of specific viral antigens, not only in virus preparations but also in cell homogenates with a threshold of detection of about 10^5 virus particles.

5044 GENETIC RELATIONSHIP OF A PRIMATE RNA TUMOR VIRUS GENOME TO GENES IN NORMAL MICE.

(Eng.) Wong-Staal, F. (Nat'l. Cancer Inst., Lab. of Tumor Cell Biology, Bethesda, Md. 20014); Gallo, R. C.; Gillespie, D. *Nature* 256(5519):670-672; 1975.

The genetic origin of simian sarcoma virus (SiSV), isolated from a woolly monkey and passaged in marmosets, was investigated by hybridization of ^{125}I -RNA (70S) from SiSV to DNA purified from a variety of animal tissues or cultured cell lines (mice, rats, Old and New World primates, pig, squirrel, cat, chicken, racoon, and slug). The condition of hybrid detection most suitable for detecting imperfect complexes formed by SiSV and cell RNA was treatment of the hybridization mixture with 20 $\mu\text{g}/\text{ml}$ RNase in 0.6 M NaCl. DNA from mice or rats hybridized more SiSV RNA than did DNA from other lower animals, but appreciable hybridization was obtained with DNA from some Old World primates and, to a lesser extent, from New World monkeys. DNA from chimpanzees hybridized only 5-10%. DNA from the lower animals, excluding mice and rats, hybridized only 1-10% of the RNA. Double reciprocal analysis of hybridization results obtained with different RNA/DNA ratios confirmed the close homology between SiSV RNA and mouse DNA. The findings indicate that SiSV may have originated in mice and subsequently entered primates; the weaker homology between SiSV RNA and primate DNA would reflect genetic changes promoted by recombination with the new host.

5045 VISUALIZATION OF ONCORNAVIRUS SUBUNITS BY ELECTRON MICROSCOPY [abstract]. (Eng.)

Weber, G. H. (Nat'l. Cancer Inst., Bethesda, Md.); Heine, U. I.; Cottler-Fox, M.; Stephenson, M. L.; Zamecnik, P. C. *Proc. Am. Assoc. Cancer Res.* 16:25; 1975.

5046 GLIOMAS INDUCED BY AVIAN SARCOMA VIRUS (ASV): EARLY AND SEQUENTIAL STRUCTURAL

EVENTS OF THE NEOPLASTIC TRANSFORMATION *IN VIVO* [abstract]. (Eng.) Vick, N. A. (Univ. Chicago, Chicago, Ill.); Bigner, D. D. *J. Neuropathol. Exp. Neurol.* 34(1):99-100; 1975.

5047 ADDITIVE ONCOGENIC EFFECTS OF AVIAN SARCOMA VIRUS AND ETHYLNITROSOUREA [abstract].

(Eng.) Swenberg, J. A. (Upjohn Co., Kalamazoo, Mich.); Bigner, D. D.; Hall, T. L.; Harbach, P. R. *J. Neuropathol. Exp. Neurol.* 34(1):99; 1975.

5048 VIRUS-LIKE PARTICLES OBSERVED IN RAT CENTRAL NERVOUS SYSTEM (CNS) TUMORS INDUCED WITH

BRATISLAVA-77 AVIAN SARCOMA VIRUS (B77-ASV) [abstract]. (Eng.) Cloyd, M. W. (Duke Univ., Durham, N.C.); Burger, P. C.; Bigner, D. D. *J. Neuropathol. Exp. Neurol.* 34(1):99; 1975.

5049 PARTIAL PURIFICATION AND CHARACTERIZATION OF N^2 -GUANINE RNA METHYLTRANSFERASE ASSOCIATED WITH AVIAN MYELOBLASTOSIS VIRUS [abstract]. Taylor, M. J. (Nat'l. Cancer Inst., Bethesda, Md.); Gantt, R. *Proc. Am. Assoc. Cancer Res.* 16:89; 1975.

5050 DIFFERENTIAL *IN VITRO* PRODUCTION OF BIOLOGICAL PROPERTIES OF RAUSCHER MURINE

LEUKEMIA VIRUS [abstract]. (Eng.) Robinson, O. R., Jr. (Nat'l. Cancer Inst., Frederick, Md.); Johnson, R. W.; Perry, A.; Shibley, G. P.; Hatgi, J. N.; Gruber, J. *Proc. Am. Assoc. Cancer Res.* 16:90; 1975.

5051 PURIFICATION AND PROPERTIES OF RAUSCHER LEUKEMIA VIRUS DNA POLYMERASE [abstract].

Modak, M. J. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.); Marcus, S. L. *Proc. Am. Assoc. Cancer Res.* 16:175; 1975.

5052 ACTIVATION OF C-TYPE VIRUSES IN CULTURED BALB/c MOUSE CELLS BY X-RAY IRRADIATION

[abstract]. (Eng.) Cardoso, E. A. (Institut de Recherches sur les Leucemies, Laboratoire d'Hematologie Experimentale, Hopital Saint-Louis, 75010 Paris, France); Saal, F.; Feuillette, A.; Peries, J. *IRCS Med. Sci.* 3(9):446; 1975.

5053 SEPARATION OF TEMPERATURE SUSCEPTIBLE MUTANT OF MOUSE SARCOMA VIRUS (MSV-MIV

complex) [abstract]. (Jpn.) Yuasa, Y. (Inst. Medical Sci., Tokyo Univ., Tokyo, Japan); Shimojo, H. *Virus (Tokyo)* 24(3):281; 1975.

5054 NONPRODUCER HUMAN CELLS INDUCED BY MURINE SARCOMA VIRUS [abstract]. (Eng.) Rhim,

J. S. (Microbiol. Assoc., Inc., Bethesda, Md.); Cho, H. Y.; Kim, E. B.; Huebner, R. J. *Proc. Am. Assoc. Cancer Res.* 16:30; 1975.

5055 MAYTANSINE AND GELDANAMYCIN INHIBITION OF TRANSFORMATION OF MOUSE CELL CULTURES

INFECTED WITH MURINE SARCOMA VIRUS [abstract]. (Eng.) O'Connor, T. E. (Nat'l. Inst. Health, Bethesda, Md.); Adrich, C.; Hadidi, A.; Lomax, N.; Okano, P.; Sethi, S.; Wood, H. B. *Proc. Am. Assoc. Cancer Res.* 16:29; 1975.

5056 DETECTION OF OLIGONUCLEOTIDE SEQUENCES THAT COMPLEMENT c-DNA OF A MURINE ONCORNA-

VIRUS IN POLY A(+) RNAs OF HUMAN LEUKEMIC CELLS [abstract]. (Eng.) Larsen, C. J. (Hopital St. Louis, 75010, Paris, France); Marty, M.; Tavitian, A.; Hamelin, R.; Peries, J.; Boiron, M. *Proc. Am. Assoc. Cancer Res.* 16:202; 1975.

5057 ONCOGENICITY OF WILD TYPE AND MUTANT STRAINS OF POLYOMA [abstract]. Siegler,

R. (Drew Postgrad. Med. Sch., Los Angeles, Calif.); Benjamin, T. *Proc. Am. Assoc. Cancer Res.* 16:99; 1975.

- 5058 POLYOMA- AND SV40-SPECIFIC MESSENGER RNAs [abstract]. (Eng.) Salomon, C. (Dept. Biologie Moleculaire, Univ. Geneve, CH-1211 Geneve 4, Switzerland); Weil, R. *Experientia* 31(6):746; 1975.
- 5059 MORPHOLOGICAL MODIFICATION OF A VIRUS-INDUCED LYMPHATIC LEUKEMIA BY THYMECTOMY AND ANTILYMPHOCYTE SERUM [abstract]. (Eng.) Dresler, S. L. (Univ. Oregon Med. Sch., Portland, Oreg); Dawson, P. J.; Fieldsteel, A. H. *Proc. Am. Assoc. Cancer Res.* 16:52; 1975.
- 5060 Fv-2-MEDIATED RESISTANCE TO FRIEND MOUSE LEUKEMIA VIRUS [abstract]. (Eng.) Blank, K. J. (Albert Einstein Coll. Med., Bronx, N.Y.); Steeves, R. A.; Lilly, F. *Proc. Am. Assoc. Cancer Res.* 16:56; 1975.
- 5061 ANTIGENIC RELATIONSHIPS BETWEEN FRIEND LEUKEMIA VIRUS AND HUMAN LEUKEMIA ASSOCIATED ANTIGENS [abstract]. (Eng.) Mohanakumar, T. (Duke Univ. Med. Cent., Durham, N.C.); Bolognesi, D. P.; Metzgar, R. S. *Proc. Am. Assoc. Cancer Res.* 16:68; 1975.
- 5062 INHIBITION OF FRIEND LEUKEMIA CELLS DIFFERENTIATION BY INTERFERON [abstract]. (Eng.) Rossi, G. B. (Istituto Superiore di Sanita OO.RR., 00161 Rome, Italy); Benedetto, A.; Grappelli, C.; Matarese, G. P. *Proc. Am. Assoc. Cancer Res.* 16:101; 1975.
- 5063 THE EFFECT OF FRIEND VIRUS INFECTION ON GRANULOCYTE EXUDATION IN RESPONSE TO ANTIGEN [abstract]. (Eng.) McGarry, M. P. (Roswell Park Mem. Inst., Buffalo, N.Y.); Mirand, E. A. *Proc. Am. Assoc. Cancer Res.* 16:191; 1975.
- 5064 LEUKOCYTIC DIFFERENTIATION IN FRIEND LEUKEMIA INDUCED BY COLONY-STIMULATING ACTIVITY [abstract]. (Eng.) Golde, D. W. (Univ. California Los Angeles Sch. Med.); Faille, A.; Sullivan, A.; Friend, C. *Proc. Am. Assoc. Cancer Res.* 16:13; 1975.
- 5065 MASON-PFIZER MONKEY VIRUS (MPMV): A HORIZONTALLY TRANSMITTED ONCORNAVIRUS OF RHESUS MONKEYS [abstract]. (Eng.) Colcher, D. M. (Meloy Lab., Inc., Springfield, Va.); Schochetman, G.; Schlom, J. *Proc. Am. Assoc. Cancer Res.* 16:22; 1975.

See also:

- * (Rev): 4833, 4834, 4835, 4844
- * (Chem): 4884, 4885, 4906, 4942
- * (Immun): 5068, 5071, 5083, 5092, 5093, 5097, 5098, 5106, 5120, 5127, 5152, 5153, 5162, 5163
- * (Path): 5275
- * (Epid-Biom): 5277

- 5066 *IN VITRO* PRODUCTION OF TRANSFER FACTOR BY LYMPHOBLASTOID CELL LINES. (Eng.) Viza, D. (Laboratoire d'Immunobiologie, Pathologie Générale et Expérimentale, Faculté de Médecine Pitié-Salpêtrière, Paris, France); Goust, J. M.; Moulias, R.; Trejdosiewicz, L. K.; Collard, A.; Müller-Berat, N. *Transplant. Proc.* 7(1/Suppl. 1): 329-333; 1975.

A technique for the *in vitro* production of transfer factor (TF) by lymphoblastoid cell lines in which the immunological activity and specificity of TF is maintained was demonstrated. Peripheral blood lymphocyte dialysable transfer factor (PBTF) and cultured cell dialysate (CCTF) were compared as measured by ribonucleotide estimation. Lymphoblastoid lines of normal (N1 and N2) and malignant (M1 leukemia line and M2 Burkett lymphoma line) origins were used. Cells ($4-5 \times 10^5 \times \text{ml}^{-1}$) were suspended in medium and PBTF was added; samples of about 10^8 cells were taken each week for 4-5 wk. The UV absorption profiles of lymphoblastoid cell-line dialysates were similar to those obtained from peripheral blood dialysates. After induction with PBTF, no difference in the optical density 260/280 nm ratio was observed, nor was there any increase in ribose concentration for the M1 and M2 cell lines. There was a marked increase of dialysable ribonucleotide concentration for N1 and N2 lines accompanied by an increase in the 260/280 nm ratio. Column chromatography yielded five main fractions for PBTF and five to six for (CCTF); the distribution of CCTF was not altered after PBTF induction. A fraction (II) common to PBTF and CCTF from lines N1 and N2 was found containing a substance of about 4,000 molecular wt. PBTF (100 μg ribose/animal) injected in rats caused the previously negative skin to become positive to the antigen test. CCTF from uninduced cells and from PBTF-induced M1 line did not modify skin tests. However, CCTF from N1 and N2 after induction showed similar results to PBTF. In baboon lymphocyte stimulation tests, incorporation of thymidine was four times greater in lymphocytes cultured with PBTF and purified protein derivative (PPD) than in those incubated with medium alone, or with PBTF or PPD only. CCTF from N1 after induction caused a four-fold increase in thymidine uptake, whereas CCTF from uninduced cells and from induced M1 cells had no effect. Although the results did not establish a dose-effect relation, it appears that in interspecies skin tests there is a threshold concentration of TF below which systemic response are not produced. The authors conclude that this technique can provide access to the necessary amounts of a standardized product for biochemical and clinical investigation.

- 5067 INDUCTION OF F_1 HYBRID ANTIPARENT CYTOTOXIC EFFECTOR CELLS: AN *IN VITRO* MODEL FOR HEMOPOIETIC HISTOINCOMPATIBILITY. (Eng.) Shearer, G. M. (Natl. Cancer Inst., Bethesda, Md. 20014); Cudkowicz, G. *Science* 190(4217):890-893; 1975.

An *in vitro* system has been developed in which F_1 spleen cells can generate cytotoxic activity directed specifically against parental cells. *In vitro* tests

of F_1 antiparent cytotoxicity were consistently correlated with the results of *in vivo* tests of the susceptibility of different irradiated F_1 hybrids to bone marrow grafts from parental strain mice. The antigenic differences detected are controlled by the H-2D-Hh-1 region of the murine major histocompatibility complex. The parent- F_1 combinations demonstrating F_1 antiparent activity *in vitro* are the same as those demonstrating F_1 rejection of parental hemopoietic grafts *in vivo*. Thus, the F_1 antiparent cytotoxicity test serves as an *in vitro* model for the recognition and effector phases of hybrid resistance to parental hemopoietic grafts and may be of value in clinical transplantation.

- 5068 THE MAJOR CELL SURFACE GLYCOPROTEIN OF CHICK EMBRYO FIBROBLASTS IS AN AGGLUTININ. (Eng.) Yamada, K. M. (Natl. Cancer Inst., Bethesda, Md. 20014); Yamada, S. S.; Pastan, I. *Proc. Natl. Acad. Sci. USA* 72(8):3158-3162; 1975.

The ability of a major cell surface protein (CSP) of chick embryo cells, to agglutinate sheep RBC was studied. We have isolated CSP from chick embryo fibroblasts by extraction with 1 M urea. These preparations of CSP agglutinated formalinized sheep RBC at protein concentrations of under 2 $\mu\text{g}/\text{ml}$. In extracts of chick embryo cells, the quantity of such hemagglutinating activity was parallel to that of CSP determined by electrophoresis, and both were markedly decreased in chick cells transformed by the Bryan high-titer strain of Rous sarcoma virus. Both CSP and hemagglutinating activity were progressively adsorbed onto RBC and could be released by 1 M urea. An antiserum to purified CSP specifically blocked the agglutination. The agglutinating activity was destroyed by boiling or treatment with proteases. The agglutinating reaction was inhibited by the chelating agents EDTA and EGTA [ethyleneglycol-bis(8-aminoethyl ether)*N,N'*-tetraacetic acid]. Agglutination was inhibited to a lesser degree by amino sugars and other amines, increased osmolarity, and urea. Other monosaccharides, hyaluronidase, DNase, and RNase had little or no effect on the agglutination reaction. This demonstration that CSP has an agglutinating activity sensitive to proteases and requiring divalent cations suggests that this molecule may play a role in cell adhesion. This information should provide an approach to the study of decreased CSP as a possible cause of decreased cell-cell adhesion of tumor cells *in vitro*. The hemagglutination assay is a rapid simple assay for CSP.

- 5069 ATOPY AND CANCER. (Eng.) Bilek, O. (Pediatric Res. Inst., 662 62 Brno-Cerna Pole, Czechoslovakia); Munzarova, M.; Zahalkova, M. *Neoplasma* 22(4):441-444; 1975.

The possible relationships between the frequencies of atopy and cancer within families was studied. The study group consisted of 1591 patients with documented hay fever. The control group consisted of 2001 persons randomly chosen without atopy or malignancy. Both groups were questioned as to the occurrence of malignancy in parents, siblings,

grandparents, aunts and uncles, and first cousins. The study group was further subdivided into two groups: A: no atopy among relatives - 660 patients; B: atopy among at least two or more relatives - 395 patients. Comparison of the whole group of atopic persons with controls revealed no statistically significant differences. In comparing group B with group A and with controls there were 195 malignancies among group B relatives, 283.7 among group A relatives and 282.8 among control relatives. It was previously found that immunoglobulin E levels are lower in most cancer patients than in healthy controls. While no firm conclusions can be made, malignancies were seen less frequently among relatives of atopic patients than in the relatives of controls.

5070 STUDIES ON THE IMMUNE STATUS OF PATIENTS WITH RENAL ADENOCARCINOMA. (Eng.) Brosman, S. (Harbor General Hosp., Torrance, Calif.); Hausman, M.; Shacks, S. J. *J. Urol.* 114(3):375-380; 1975.

Thirty-one patients (23 men and eight women) with renal carcinoma were evaluated with skin tests to determine cell-mediated immunity, and an *in vitro* chemotaxis assay was used to measure monocyte function. The control population consisted of 20 healthy volunteers (14 men and six women) and 12 patients (10 men and two women) hospitalized with nonmalignant disease of the upper urinary tract. The patients were divided into one of three groups depending upon the tumor stage: (1) localized tumor, (2) locally invasive disease, or (3) metastatic disease. The patients were treated with id inoculations (0.1 cm³) of a battery of recall antigens (i.e., mumps, monilia, streptokinase-streptodornase, and purified protein derivatives) and dinitrochlorobenzene (DNCEB) and croton oil. Monocyte chemotactic response was significantly depressed in the patients when compared to the controls (-1.93±0.41 versus 1.95 to -1.25, respectively). The defect was more severe in patients with advanced disease. The monocyte function improved following nephrectomy (at three months, -1.17±0.32, and -0.55±0.22 at six months postoperatively) in patients with localized disease. Patients with advanced disease had fewer positive reactions to recall antigens, DNCEB, or croton oil, than did the controls or those with localized disease. The results demonstrate that renal adenocarcinoma patients have a defect in cellular immunity and inflammatory response. The authors conclude that monocyte chemotactic response is a reliable and useful measure of monocyte function, and it correlates with the clinical stage of renal carcinoma.

5071 FAILURE TO DETECT ANTI-GROUP-SPECIFIC MURINE LEUKEMIA VIRUS ACTIVITY IN TETRAPARENTAL AKR-CBA CHIMERAS. (Eng.) Barnes, R. D. (Clinical Res. Centre, Harrow, Middlesex HA1 3UJ, England); Tuffrey, M. A.; Bourne, R. C. *Cancer Res.* 35(10):2699-2703; 1975.

Tetraparental AKR-CBA/H-T6 mouse chimeras were derived and investigated to determine whether factors associated with the tumor resistance of the CBA/H-

T6 mouse could overcome the innate lymphoma susceptibility of the AKR mouse. Gross (gs) antigen present in the sera of both AKR and AKR-CBA/H-T6 chimeras was quantitated by an indirect two-stage immunofluorescent absorption assay. Indirect absorption was used to demonstrate the lack of anti-murine leukemia virus - gs in the sera. Two AKR control serum pools had relatively high titers of gs, while no activity was demonstrated in a single pooled CBA serum sample. When gs antigen levels were determined in the chimera serum, reciprocal titers of 1-16 were obtained. There was no obvious association between gs titer and the development of lymphoma; however, titers were greater in the predominantly albino AKR mice. Incubation of the gs antigen from an AKR serum pool with an aliquot of murine leukemia virus-gs serum reduced the titer in the immunofluorescent assay from 1:512 to 1:126, suggesting that the gs antigen was complexed to mouse immunoglobulin (Ig). The antigenicity of gs was unaltered in the chimera following treatment with anti-Ig-coupled Sepharose, suggesting that the gs antigen was free. Coated Sepharose particles used for absorption failed to neutralize the anti-murine leukemia virus-gs serum, supporting the lack of binding of the gs antigen. Thus, the data favors the existence of free gs antigen, and in turn, the absence of anti-gs antibody activity in the chimera.

5072 LYMPHOCYTE STIMULATION BY A MAMMARY CARCINOMA ASSOCIATED GLYCOPROTEIN. (Eng.) Hakim, A. A. (Univ. of Illinois at the Medical Center, Chicago, Ill. 60680). *Immunol. Commun.* 4(3):251-273; 1975.

A glycoprotein (GPCAA) was isolated from 3 M KCl extracts of human mammary carcinoma. The activation of DNA-polymerase in human blood lymphocytes by the addition of GPCAA to the culture medium was measured by [³H]thymidine uptake. In addition, a blocking factor was obtained from the isotonic glycine-NaCl buffer (pH 3.1) extracts of human mammary carcinoma cell membranes. Lymphocytes were isolated from the peripheral blood of ten normal volunteers and from five patients with mammary carcinoma. The results of several physico-chemical analyses indicated that the purified carcinoma-associated antigen was a glycoprotein: (a) the antigen showed a sharp peak absorbing between 279 to 281 nm; (b) digestion with trypsin followed by filter paper resolution, produced ninhydrin reacting compounds; (c) upon treatment with *Vibrio cholera* neuraminidase, sialic acid was released; (d) when incubated with collagenase, followed by chromatographic resolution, it produced compounds that react with anthrone sulfuric acid, and phenol-sulfuric acid and gave a characteristic orange-red color with orcinol; and (e) interaction with diphenylamine sulfuric acid gave a blue color. The positive cytotoxicity, *in vitro*, of rabbit antisera (at dilutions greater than 1:160) immunized with mammary carcinoma cells or GPCAA against the carcinoma cells indicated that the antigenic glycoprotein was associated with the mammary carcinoma and not a component of normal human serum. Addition of an optimal amount of GPCAA induced proliferation of peripheral blood lymphocytes from both normal donors and from patients with mammary carcinoma. RNA-dependent DNA-polymerase levels were markedly in

increased in GPCAA-untreated lymphocytes from patients with mammary carcinoma and in GPCAA-treated mammary lymphocytes of both normal donors and tumor-bearing patients. Addition of an optimal amount of the blocking factor inhibited the GPCAA-induced stimulation of the RNA-dependent DNA-polymerase activity in the GPCAA-treated lymphocytes of both normal donors and tumor bearing patients. The authors suggest that this synthetic reaction (RNA-instructed DNA synthesis) may be important for cellular differentiation and the secondary immune response.

- 5073 HUMORAL IMMUNOSTIMULATION: V. SELECTION OF VARIANT CELL LINES. (Eng.) Shearer, W. T. (Washington Univ. Sch. Medicine, St. Louis, Mo. 63110); Parker, C. W. *J. Exp. Med.* 142(5):1133-1149; 1975.

In order to gain insight into the long-term effects of stimulation amounts of antibody upon cell growth and metabolism, L-cells were grown *in vitro* in the presence of anti-L-cell antibody for several months. A permanent L-cell variant cell line (LC₁) was isolated by the growth of the parent L-cell line (L) in the presence of a cytostimulatory dose (1:200) of rabbit anti-L-cell antiserum (AL) for nine months. LC₁ differed from L in many aspects: (a) it was larger (1,533 mm³ versus 1,284 mm³), (b) it grew faster (1.5- to 2-fold), (c) it grew in aggregated fashion, (d) its growth was no longer stimulated by AL, (e) it was almost completely resistant to high concentrations of AL in the presence of complement (C), (f) its original membrane antigens (immunogenic for AL) were redistributed in sparse and patchy clumps as noted by fluorescence microscopy, (g) it contained about 65% of the total original ¹²⁵I-AL membrane-binding sites (1.4 x 10⁷/cell versus 2.2 x 10⁷/cell), (h) its AL-binding sites displayed a lower average affinity constant (K = 0.9 x 10⁵ M⁻¹ and (i) it contained a smaller proportion of high affinity K > 10⁶ M⁻¹ binding sites (13% versus 21%). LC₁ was fully immunogenic in that it was readily killed by homologous antiserum (ALC₁) and C, whereas L was not similarly affected by ALC₁; this indicates that C₁ contained new membrane antigens not present on L. Another variant (LC₂) was produced by growth of C₁ in a 10-fold higher dose (1:20) of AL (cytotoxic or L) for one month. LC₂ was even more resistant to AL in the presence of C, contained 0.84 x 10⁷ AL-binding sites/cell with an average affinity constant of 1 x 10⁵ M⁻¹ (unchanged from LC₁), and was less susceptible than LC₁ to lysis in the presence of ALC₁ and C. These findings confirm and extend previous *in vitro* and *in vivo* observations dealing with the direct stimulation effects of antibody on tumor cell metabolism. The results suggest that immunostimulation may be a mechanism of tumor escape from immune control *in vivo*, possibly by immunoselection and antigenic modulation.

- 5074 SPECIFICITY OF THE IMMUNE RESPONSE IN AN L-5178Y-DBA/2 SYNGENEIC MOUSE SYSTEM. (Eng.) Goldstein, L. T. (Wistar Inst., Philadelphia, Pa.); Manson, L. A. *Transplant. Proc.* 7(1/Suppl. 1): 13-515; 1975.

The specificity of the immune response generated by the DBA/2 host to syngeneic and allogeneic normal tissues and tumor lines was investigated. L-51784, P815, and L-1210 lines were carried as an ascites in DBA/2 female mice by weekly i.p. transfer. EL-4 leukemia was carried in C57BL/6J mice by weekly i.p. transfer and in tissue culture in RPMI-1640. Antibodies were detected by radioimmunoassay, and "killer" cells were assayed by microcytotoxicity tests. P815 and EL-4 cell lines immunized DBA/2 mice to reject a lethal challenge of L-5178Y tumor. No immunity was induced by normal DBA/2 spleen or thymus cells, presenting a tumor-associated transplantation antigen. Immunized DBA/2 which have rejected a live tumor challenge contained in their sera noncytolytic antibodies (detected by radioimmunoassay and a cell-binding assay) directed against tumor-associated antigens. The serum cross-reacted to a significant extent with the three tumor cell lines and to a lesser extent with DBA/2 thymocytes. Normal DBA/2 sera showed some binding to the cell lines and almost none to normal DBA/2 thymocytes. Killer cells induced against L-5178Y cross-reacted only with P815 tumor. Killer cells induced *in vitro* against allogeneic EL-4 tumor did not react significantly against the L-5178Y tumor. The actual and relative roles of antibody and killer cells in tumor rejection are still unknown. The authors suggest that in order to rationalize the cross-protection observed *in vivo* with the specificities of the humoral and cell-mediated responses, studies of the L-5178Y and comparable systems must be pursued.

- 5075 H-2-LINKED Ir GENES CONTROLLING IMMUNE RESPONSES TO BALB/c IgG (γ2a) MYELOMA PROTEINS HAVING κ OR λ LIGHT CHAINS. (Eng.) Lieberman, R. (Natl. Cancer Inst., Bethesda, Md.); Paul, W. E.; Humphrey, W., Jr.; Potter, M. *Transplant. Proc.* 7(1/Suppl. 1):115-118; 1975.

The possibility that the same H-2 linked Ir gene is involved in immune responses to all BALB/c immunoglobulin G (IgG) proteins of the same class was investigated. Inbred, H-2-cogenic, and recombinant strains were studied for their response to four kappa-type IgG myeloma proteins (MOPC173, LPC1, UPC10, and RPC5) and two lambda-type myeloma proteins (HOPCO and S5444). No antibody response was observed in inbred mice with the same allotype as BALB/c. In strains with allotypes different from BALB/c, a high immune response was found in H-2 types b, r, s, and v for two to three of the kappa-type myeloma proteins and for both the lambda types. Results with B10-cogenic strains and H2^a/H2^b recombinant strains indicated that regardless of the V_H region of the myeloma protein, the same Ir gene (Ir-1^b) is employed in the immune response to BALB/c kappa-type myeloma proteins. A high response to the kappa myeloma proteins was found in H-2^b (B10) and a low response in H-2² (B10.A). Among the H-2^a/H-2^b recombinants, B10.A (1R) and B10.2 (2R) gave a low response and B10.A (4R) and B10.A (5R) gave a high response. The response of 4R for UPC10 or RPC5 was less than that of 5R or B10. All the recombinants tested gave little or no response to the lambda-type protein S5444, while B10 gave an ex-

cellent response. That the immune response to HOPC1 was linked to H-2 was shown by the very high response of B10.M mice to this protein. The recombinants also gave low responses to HOPC1. The data support the concept that genetic control of responsiveness to kappa-type IgM myeloma proteins involves recognition of constant-region allotypic-associated determinants.

- 5076 ALLOGRAFT ENHANCEMENT BY DIFFERENT MECHANISMS IN MICE IMMUNIZED WITH PAPAIN-SOLUBILIZED TRANSPLANTATION ANTIGEN. (Eng.) Zola, H. (Dept. Experimental Immunobiology, Wellcome Res. Lab., Beckenham, Kent, England). *Transplant. Proc.* 7(1/Suppl. 1):449-450; 1975.

Two regimes that enhanced growth of the RI tumor (a CBA leukemia) and death of the mice (25 U transplantation antigen ip 7 days before challenge; single-pulse course) and (25 U ip on day 0 and on day 28, challenge on day 42; 2-pulse course) were studied. Cell-mediated cytotoxicity (CMC) was measured using peritoneal lymphocytes and CBA spleen target cells. The single-pulse course suppressed *in vitro* CMC, whereas the two-pulse course elevated it. Mice given the single-pulse course showed a target-cell blocking activity in the serum after immunization that disappeared on challenge. The serum taken 5 days after challenge contained effector-cell blocking but not target-cell blocking activity. In mice immunized by the 2-pulse course target-cell blocking activity fell after challenge. The serum taken 5 days after challenge had both target-cell and effector-cell blocking activities. The eluate inhibited cytotoxicity if added to the mixture. It did not block CMC if either effector or target cells were pretreated with it. Evidence of blocking antibody on the enhanced tumor cells 5 days after challenge was shown by indirect immunofluorescence, reduced capacity of the cells to absorb C57BL anti-CBA antibody, reduced requirement for added allo-antibody to cause complement-mediated lysis, and by the resistance of enhanced cells to lysis by immune lymphocytes. Cells from mice given the 2-pulse course showed greater blocking activity. Blocking antibody was eluted from the tumor cells of mice given the single-course pulse but not those given the 2-pulse course.

- 5077 TIME-LAPSE CHANGES IN THE CONCOMITANT IMMUNITY OF LYMPHOCYTES FROM DIFFERENT SITES OF MICE ISOGRAFTED WITH METHYLCHOLANTHRENE-INDUCED TUMOR. (Eng.) Orita, K. (Okayama Univ. Medical Sch., Okayama, Japan); Ohnishi, N.; Matsuo, Y.; Konaga, E.; Kokumai, Y.; Tanaka, S. *Acta Med. Okayama* 29(2):85-91; 1975.

The isografting of methylcholanthrene-induced tumor (MC-tumor) sc on the back of C3H mice is described. The regional axillary lymph nodes, spleen and distant mesenteric lymph nodes were removed from these animals 1, 2, 3, and 4 wk later. Lymphocytes prepared from these lymphatic tissues with primary MC-tumor culture cells were mixed and cultured together to estimate antitumor activity of lymphocytes from different sites. A strong antitumor activity was seen only in those regional axillary lymph node cells

taken out one or two wk after tumor transplantation. The activity was weakened by three or four wks. On the other hand, distant mesenteric lymph node cells one or two wk after the transplantation had no antitumor activity, while at the terminal cancer stage of four wk a stronger antitumor activity than that of regional lymph nodes appeared. In the spleen, a strong antitumor activity was observed in the third wk after tumor transplantation, but the activity disappeared by the fourth wk. The onset of tumor and antitumor activity appears in the regional lymph nodes after tumor transplantation, and diminishes as the tumor grows larger. Activity appears in more distant lymphatic tissues.

- 5078 ALLOGENEIC INHIBITORY ACTIVITY OF REGIONAL LYMPH NODE CELLS IN THE MOUSE ISOGRAFTED WITH METHYLCHOLANTHRENE-INDUCED TUMOR. (Eng.) Orita, K. (Okayama Univ. Medical Sch., Okayama, Japan); Ohnishi, N.; Kunisada, K.; Konaga, E.; Kokumai, Y. *Acta Med. Okayama* 29(3):183-187; 1975.

The correlation between the allogeneic activity of lymphocytes and progression of cancer was studied. Methylcholanthrene-induced tumor (MC-tumor) was isografted subcutaneously on the back between scapulae of C3H mice, and the lymphocytes were prepared from the regional axillary lymph nodes removed from these mice at 1, 2, 3, or 4 wk after grafting. The lymph node cells were cultured together with 40-fold numbers of allogeneic JTC-11 cells derived from Ehrlich cancer cells cultured with phytohemagglutinin (2 mg/10 ml) 24 or 48 hr. The proliferation rate of JTC-11 cells at weekly intervals indicated the allogeneic inhibitory activity of lymph node cells. In the first or second week, regional lymph node cells showed a strong allogeneic inhibitory activity, as did lymph node cells from normal mice. Three and four wk after isografting, the inhibitory activity of regional lymph node cells was significantly lower ($P < 0.001$) than the controls.

- 5079 LYMPHOCYTE RESPONSIVENESS IN CANCER AND TRANSPLANTATION. (Eng.) McKhann, C. F. (Dept. Surgery, Univ. Minnesota, Minneapolis, Minn.); Slade, M. S.; Gunnarsson, A.; Burk, M. W. *Transplant. Proc.* 7(2):287-290; 1975.

The immune capacity of human kidney donors after surgery, of human kidney transplant recipients, of patients with untreated malignancies, and of animals bearing transplantable tumors was studied. The response capacity was assessed on the basis of *in vitro* response of the test subject's lymphocytes in the mixed lymphocyte test or to phytohemagglutinin (PHA), concanavalin A (Con-A) or pokeweed mitogen. In kidney donors, the response declined at the initiation of anesthesia, returned to normal levels during the operation, and fell significantly during postoperative hours. The capacity of the same cells to stimulate normal cells from another individual was impaired in a similar pattern, suggesting modulation of cell antigenicity or effects of circulatory factors. The capacity of peripheral lymphocytes of kidney donors to respond to nonspecific PHA and Con-A stimulation was also impaired, reach-

ing a nadir on the evening following surgery but returning to preoperative levels 4-6 days later. In kidney transplant recipients receiving imuran and prednisone a few hours prior to transplantation, the period surrounding the time of transplantation was associated with an abrupt drop in the number of circulating T and B cells and in the corresponding capacity of the circulating cells to respond to appropriate mitogens *in vitro*. These cells regain about 70% of their normal responsiveness by two weeks post-transplantation. In patients with untreated malignancies, skin tests and *in vitro* tests with mitogens showed immune depression in 8/8 patients with colon carcinoma; 5/7 with lung carcinoma; 6/10 with sarcomas; 12/25 with melanoma; and 6/15 with cervical carcinoma. In mice bearing transplantable methylcholanthrene-induced sarcomas, it was found that at 14 days, when the tumor reached a size of 1 cm in diameter, the response of the host's lymph node cells to stimulation by the tumor cells *in vitro* increased dramatically. Prior to that time, the response increased gradually; subsequently, it decreased gradually. When the growing tumor was removed, within about a week the lymph node cells regained their capacity to respond to stimulation *in vitro*. These findings were interpreted as indicating that after 14 days the pool of cells capable of responding was exhausted and that those that had been stimulated were essentially refractory to further stimulation. Their return to normal activity following removal of the tumor probably represented repopulation with new, unstimulated cells. Further work indicated that the immunosuppression of the lymphocytes could be explained by the excessive production of tumor antigen, causing the immune response to be overcome. The mechanism of nonspecific suppression, however, was much more difficult to explain, although it was speculated that the possibility again existed that large amounts of circulating antigen were involved.

5080 RESTORATION OF SPECIFIC IMMUNITY AGAINST SV40 TUMOR-SPECIFIC TRANSPLANTATION ANTIGEN TO LYMPHOID CELLS FROM TUMOR-BEARING MICE. (Eng.) Blasecki, J. W. (Univ. Mississippi Medical Center, 2500 North State St., Jackson, Miss. 39216); Tevethia, S. S. *Int. J. Cancer* 16(2):275-283; 1975.

Specific cell-mediated immunity to simian virus 40 (SV40) tumor-specific transplantation antigen (TSTA) in BALB/c mice undergoing progressive tumorigenesis by syngeneic SV40-transformed cells (VLM) was investigated *in vivo* using a tumor-cell neutralization test. The method involved the preparation of cell suspensions from mouse spleens and peritoneal exudates (the latter prepared by ip inoculation of paraffin oil). The suspension was mixed with an equal volume of tumor cell suspension to give the effector:target cell ratios desired. The mixtures were incubated for 30 min at 37 C, and 0.2 ml was inoculated sc into normal BALB/c mice. Specific cellular reactivity to SV40 TSTA was not detected in BALB/c mice bearing large tumors (10-15 mm mean diameter), but was demonstrable after tumor excision. Specific cytotoxic reactivity against syngeneic SV40-transformed cells *in vivo* was restored to lymphoid cells from VLM tumor-bearing mice either by culturing the lymphoid cells *in vitro* or by treating them with

papain (0.1 mg/ml) or trypsin (0.001 mg/ml). Enzyme-treated lymphoid cells from methylcholanthrene tumor-bearing BALB/c mice had no cytotoxic reactivity against VLM cells. These results suggest that tumor-bearing hosts possess lymphocytes that are sensitized to the TSTA of the tumor, but that the reactivity of these lymphocytes is blocked.

5081 CELL MEDIATED IMMUNITY IN HUMAN OSTEOGENIC SARCOMA. (Eng.) Agashe, S. S. (Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay-12, India); Nair, P. N. M.; Rao, R. S.; Gangal, S. G. *Indian J. Cancer* 12(1):61-66; 1975.

The cell-mediated immunity of four human osteogenic sarcomas and of two lines derived from normal periosteal fibroblasts to autochthonous and allogeneic osteosarcoma cells was investigated *in vitro* by the ⁵¹Cr release assay, and by a microcytotoxicity assay. Attacker WBC were collected from blood samples of 17 osteogenic sarcoma patients, of two patients with Ewing's tumor; six samples were also obtained from the patient's relatives. The ⁵¹Cr release assay demonstrated positive cytotoxicity against two osteogenic sarcoma cell lines in 13 of 27 reactions (48%). These included one autochthonous reaction and two allogeneic reactions of lymphocytes from the two Ewing's tumor patients. Six of 11 reactions (54%) of lymphocytes from the sarcoma patients' relatives showed positive cytotoxicity by this technique. The microcytotoxicity assay revealed 94% (34/36) positive cytotoxicity of lymphocytes from osteosarcoma cell lines and 45% (8/17) positivity in normal cells. Fifty-five percent of the lymphocyte samples, therefore, showed true tumor-specific cytotoxicity.

5082 RETICULUM CELL SARCOMA: AN EFFECTOR CELL IN ANTIBODY-DEPENDENT CELL-MEDIATED IMMUNITY. (Eng.) Ralph, P. (Salk Inst. Biol. Stud., San Diego, Calif.); Prichard, J.; Cohn, M. *J. Immunol.* 114(2):898-905; 1975.

A transplantable, murine reticulum cell sarcoma is described. Initially arising in a female BALB/c/NIH mouse, the tumor (J774) was ascitic. Experiments were performed with cells from passages 7-24 and included an erythrocyte antigen-binding assay and a chromium release assay for antibody-directed cytotoxicity. The J774 tumor was characterized by metastases to all abdominal organs and lungs and appeared microscopically identical to the type A reticulum cell sarcoma. It readily took up rec stain and carbonyl iron. Specific binding of SREC or burro RBC by J774 cells in the presence of appropriate mouse anti-erythrocyte sera was observed. The cells were also highly efficient in the lysis of ⁵¹Cr-labeled SRBC in the presence of rabbit or mouse anti-SRBC serum, releasing 50-77% of the radioactivity. The J774 cells were five times as active as spleen cells in lysing RBC in the presence of the appropriate antiserum. Special tests precluded the possibility that such antibody-dependent cytotoxicity was due to contaminating normal peritoneal cells. With the aid of myeloma proteins, aggregated with bis-diazotized benzidine and labeled with ¹²⁵I, it was found that the J774 cells bound

IgG2a and IgG2b; to a lesser extent, the cells bound IgG1, but not IgM, IgG3 or IgA. Thus, the J774 cells appear to carry receptors for IgG2a and IgG2b. The reticulum cell sarcoma line thus has a number of properties characteristic of macrophages, including adherency, phagocyticity, specific binding of antibody-coated RBC and effector cell function in antibody-dependent cytotoxicity.

- 5083 IgM ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY IN THE MOLONEY SARCOMA VIRUS SYSTEM: THE INVOLVEMENT OF T AND B LYMPHOCYTES AS EFFECTOR CELLS. (Eng.) Lamon, E. W. (Cancer Res. and Training Center, Univ. Alabama in Birmingham, Birmingham, Ala. 35294); Whitten, H. D.; Skurzak, H. M.; Andersson, B.; Lidin, B. *J. Immunol.* 115(5): 1288-1294; 1975.

The subpopulations of effector cells involved in tumor cell destruction in the Moloney sarcoma virus (MSV) system were evaluated; tumor specific immunoglobulin (IgM) was used as the sensitizing antibody. The target cells used were Ha2, a line from an MSV-induced tumor of a CBA mouse. With unfractionated sera from adult BALB/c mice that had undergone regression of primary MSV tumors, macrophages did not contribute to the cytotoxicity induced by normal spleen cells syngeneic to the target cells. The IgM fraction of MSV regressor sera induced cytotoxicity against the target cells by immunoadsorbent column-fractionated normal spleen cells, which were either depleted of T cells or B cells, according to the specificity of the columns. Immune IgM was also found to potentiate the activity of MSV regressor spleen cells that had been similarly fractionated. Furthermore, IgM antibody was found to induce cytotoxicity by normal spleen cells which had been depleted of either T or B cells by the appropriate antiserum (anti-T or anti-Ig) in the presence of complement and subsequent recovery of the viable cells by trypsinization, filtration, and washing. However, spleen cells treated with both anti-T and anti-Ig sera simultaneously in the presence of complement and subsequent recovery of viable cells, were not induced to be cytotoxic against the IgM-coated tumor target cells. Further support of the finding that IgM antibody could induce cytotoxicity by T cells was provided by an experiment showing the induction with IgM of cytotoxicity against the target cells by normal thymocytes.

- 5084 CELL-MEDIATED CYTOTOXICITY TO HUMAN PULMONARY NEOPLASMS. (Eng.) Vose, B. M. (Dept. Immunol., Paterson Lab., Manchester, England); Moore, M.; Jack, G. D. *Int. J. Cancer* 15(2):308-320; 1975.

Peripheral blood leukocytes from patients with confirmed pulmonary neoplasia were tested for cytotoxicity against cultured cells derived from lung tumors of various histological types, fetal and normal adult lung tissue, and tumors arising in organs other than the lung. The cultured cells (100-200) were seeded into wells of microcytotoxicity plates, incubated at 37 C for 4-24 hr, and then allowed to interact with WBC suspensions at an effector to target cell ratio

of 75:1. After two days incubation the plates were washed to remove dead cells; the cells were then fixed and stained. The number of cells surviving in each well was counted, and the percentage reduction of cell survival in experimental wells compared to control (normal WBC) wells was calculated. WBC from 73% of the 26 patients were cytotoxic for lung-tumor derived cells compared with age- and sex-matched normal donors, while the frequencies of reactivity against lung-derived cells and cells from unrelated tumors (e.g. bladder, colon, breast) were 42% and 18%, respectively. WBC from lung cancer patients were also cytotoxic for cells derived from fetal lung, but susceptibility to cytolysis was variable; cells from 13- and 14-wk embryos revealed the greatest reactivity (88%). WBC from patients with a variety of tumors of nonpulmonary origin or with nonmalignant conditions (including respiratory disorders) were also reactive with lung-tumor-derived target cells, but with a lower overall frequency (35%) than those from lung cancer patients. The significance of these cytotoxicity data for the existence of tumor-specific host immunoreactivity in lung neoplasia is discussed.

- 5085 CELL-MEDIATED CYTOTOXICITY IN VITRO OF HUMAN LYMPHOCYTES AGAINST A TISSUE CULTURE MELANOMA CELL LINE (IGR3). (Eng.) Peter, H. H. (Medizinische Hochschule, Abteilung für Klinische Immunologie und Transfusionsmedizin, 3000 Hannover, Germany); Pavie-Fischer, J.; Fridman, W. H.; Aubert, C.; Cesarini, J.-P.; Roubin, R.; Kourilsky, F. M. *J. Immunol.* 115(2):539-548; 1975.

Purified peripheral blood lymphocytes from 13 healthy donors, six melanoma patients, and one halo nevus patient were tested for cytotoxic activity against an allogeneic melanoma cell line (IGR3). The lymphocytes were tested in at least one of the following assays: cell-mediated cytotoxicity (CMC), antibody-dependent cellular cytotoxicity (ADCC) and microcytotoxicity assay (MA). The lymphocytes were isolated by Ficoll-Triosil gradient centrifugation (fraction F) followed by removal of iron-phagocytosing and adherent cells (fraction FFF) and by subsequent passage through anti-IgG columns (fraction FFF-C). WBC of each fraction were identified by different methods, including morphology, rosette-formation, phagocytic activity, and membrane fluorescence. CMC activity paralleled ADCC activity at a log lower level of sensitivity. In both assays lymphocytes of fractions F and FFF had the highest activity, whereas in fraction FFF-C cytotoxicity was strongly reduced. In all three lymphocyte fractions CMC and ADCC activity could be blocked by preincubation of the effector cells in aggregated IgG. Furthermore, depletion of E rosette-forming lymphocytes slightly increased ADCC and CMC activity, whereas depletion of EA and EAC rosette-forming lymphocytes strongly decreased it. The results indicate that in both CMC and ADCC assays, nonadherent, nonphagocytic Fc receptor-bearing lymphocytes were the active cytotoxic cells. In MA, on the other hand, mononuclear phagocytes seem to have been the most active cell population. No significant differences have been so far observed in CMC, ADCC, and MA between normal subjects and melanoma patients.

- 5086 IMMUNOSUPPRESSOR T CELLS IN TUMOR BEARING HOSTS. (Eng.) Fujimoto, S. (Faculty of Medicine, Univ. of Manitoba, Winnipeg, Manitoba, Canada); Greene, M.; Sehon, A. H. *Immunol. Commun.* 4(3):201-217; 1975.

The possibility was investigated that the apparent ineffectiveness of the immune response of tumor-bearing animals (TBA) in rejecting antigenic tumors might be due to negative cellular interactions mediated by "suppressor" T cells. The experimental system consisted of two- to three-month-old A/Jax (A/J) mice, bearing a transplantable methylcholanthrene-induced tumor (sarcoma 1509a) or control tumors (lymphoma L1117 or mammary carcinoma 15091A). Immunization to the 1509a tumor was accomplished by sc injection of 10^6 cells, followed by excision of the tumor one week later. Thymus and spleen cell suspensions were prepared from mice one week after inoculation with 10^6 tumor cells. The thymus or spleen cells were transferred iv into syngeneic TBA and the presence of suppressor cells was established by measurements of inhibition of tumor rejection, based on changes in tumor size. Immune mice receiving thymus or spleen cells from normal A/J mice or from mice bearing unrelated tumors served as controls. The immunosuppressive activity of thymus or spleen cells of TBA was totally abolished by *in vitro* treatment with AKR/J anti-C3H antiserum and complement. Soluble factor(s) with identical suppressive activity was isolated from thymus cells of TBA by repeated freezing at -78°C and thawing at 37°C , followed by centrifugation at 100,000 g. The molecular size of the soluble factor was estimated to be lower than that of serum albumin in terms of its elution behavior on Sephadex G-200. It is suggested that the immunosuppressor T cells or their soluble factor(s) are largely responsible for the growth of antigenic tumors.

- 5087 IMPAIRED SYNTHESIS OF POLYCLONAL (NON-PARAPROTEIN) IMMUNOGLOBULINS BY CIRCULATING LYMPHOCYTES FROM PATIENTS WITH MULTIPLE MYELOMA: ROLE OF SUPPRESSOR CELLS. (Eng.) Broder, S. (Natl. Cancer Inst., Bethesda, Md. 20014); Humphrey, R.; Durm, M.; Blackman, M.; Meade, B.; Goldman, C.; Strober, W.; Waldmann*, T. *N. Engl. J. Med.* 293(18):887-892; 1975.

Since patients with myeloma have serious abnormalities of humoral immunity, an *in vitro* assay was used to determine the capacity of B lymphocytes to mature into immunoglobulin (Ig) secreting cells. In peripheral blood lymphocytes from 22 normal persons, geometric mean Ig synthesis during seven days in culture with pokeweed mitogen, was 4910 ng for IgM, 1270 ng for IgA and 1625 ng for IgG. The synthesis rates of peripheral blood lymphocytes of 22 patients with myeloma were 458 ng for IgM, 321 ng for IgA and 218 ng for IgG. Circulating mononuclear cells, from three of six patients tested, suppressed polyclonal immunoglobulin synthesis by co-cultured normal lymphocytes. Suppressive activity was not mediated by purified T cells alone. Removal of phagocytic mononuclear cells from lymphocyte populations of one patient nullified suppressive activity. Removal of

phagocytic mononuclear cells from lymphocyte populations of a second patient led to a nearly ten-fold increase in polyclonal immunoglobulin synthesis. Host suppressor cells may play a part in the decreased capacity of B lymphocytes to secrete immunoglobulin in certain patients with myeloma. The suppressor cells may be monocytes.

- 5088 IMMUNOSUPPRESSION IN PRIMARY LIVER AND COLON TUMOR INDUCTION WITH *N*-HYDROXY-*N*-2-FLUORENYLACETAMIDE AND AZOXYMETHANE. (Eng.) Kroes, R. (American Health Foundation, Valhalla, N.Y. 10595); Berkvens, J. M.; Weisburger*, J. H. *Cancer Res.* 35(10):2651-2656; 1975.

The question of whether immunosuppression in a rat model system would affect the carcinogenic processes leading to tumors in the liver and the large bowel was investigated. The protocols were designed to detect an increased incidence or a shorter latent period stemming from a change in immune status. Groups of male Fischer 344 rats were given purified gamma fraction of antilymphocytic serum (ALG) prior to the initiation of the carcinogen regimen (2.0 ml, twice weekly, ip) and continuously thereafter (0.5 ml, twice weekly, ip). Appropriate controls received the γ fraction of normal rabbit serum or 0.9% NaCl solution. Permanence of skin allografts showed that ALG was an effective immunosuppressive treatment. For liver cancer induction, rats were fed 120 ppm *N*-hydroxy-*N*-2-fluorenylacacetamide in the diet for 16 wk, and then were continued on control diet. The animals given ALG developed liver tumors at a rate similar to that of controls. To induce cancer of the large bowel, rats received sc doses of azoxymethane (7.5 mg/kg/wk, 16 wk), and were then held on control diet. With an identical ALG treatment, there were fewer intestinal tumors in the early part of the treatment; this was not seen in control rats given injections of 0.9% NaCl. At a later time (20-26 wk), the incidence of intestinal cancer was similar in rats on ALG or on 0.9% NaCl solution. Thus, immunosuppression has little effect on the rate of liver tumor formation with a liver carcinogen. Also, ALG leads to the precocious development of liver angiosarcomas, but fails to affect intestinal cancer induction in animals given azoxymethane.

- 5089 DERANGEMENTS OF IMMUNOGLOBULIN LEVELS, PHYTOHEMAGGLUTININ RESPONSIVENESS AND T AND B CELL MARKERS IN DOWN'S SYNDROME AT DIFFERENT AGES. (Eng.) Burgio, G. R. (Pediatric Clinic, Univ. Pavia, Pavia, Italy); Ugazio, A. G.; Nespoli, L.; Marcioni, A. F.; Bottelli, A. M.; Pasquali, F. *Eur. J. Immunol.* 5(9):600-603; 1975.

To characterize the immunodeficient status of Down's Syndrome (DS), studies were performed in 83 mongoloids, ranging in age from a few months to 30 yr, and in 76 karyotypically normal age-matched controls. Serum immunoglobulin levels of IgG, IgA and IgM, together with response of peripheral blood lymphocytes (PBL) to phytohemagglutinin (PHA), were determined in all subjects. In 51 DS and 54 controls, PBL were also tested for relative percentage of T

cells, based on capacity to form rosettes with SRBC, and for relative percentage of B cells, based on fluorescence with fluorescein-conjugated rabbit antisera to the three different immunoglobulins. Both the humoral thymus-independent and the cellular thymus-dependent functions were impaired in DS, with a characteristic age sequence as follows. Serum immunoglobulin levels were normal in DS children less than five years old; after six years of age, a definite hyperglobulinemia of the IgG and IgA type was observed. A slight decrease in IgM was observed between 16 and 25 yr of age. Lymphocyte PHA responsiveness in DS subjects was in the normal range during the first decade, but decreased progressively thereafter. The percentage and absolute number of rosette-forming PBL were abnormally low at all ages including infancy, while the number of PBL with a high density of surface immunoglobulins was always in the normal range. An observed lack of statistical correlation between PHA-responsiveness and percentage of rosette-forming PBL suggested that PHA-responsive lymphocytes and rosette-forming lymphocytes represent two distinct or at least not completely overlapping subpopulations of T cells. It is speculated that the primary immunological defect of DS involves a subpopulation of "suppressor" T cells, previous evidence having suggested that such cells play a crucial role in regulation of antibody synthesis as well as in the suppression of malignant lymphoid transformation.

- 5090 TUMOR METASTASIS IN MICE WITH REDUCED IMMUNE REACTIVITY. III. STUDIES WITH THREE WEAKLY ANTIGENIC TUMOURS IN THYMECTOMIZED AND/OR SUB-LETHALLY IRRADIATED MICE. (Eng.) Suurkula, M. (Dept. Pathol. I, Univ. Goteborg, Sweden); Boeyrd, B. *Int. J. Cancer* 16(3):404-412; 1975.

The effect of immunosuppressive treatment on the tumor metastasis of three weakly antigenic tumors was investigated in inbred CBA and C3H/HeA mice. One methylcholanthrene (MCA)-induced sarcoma (MCG12), one epidermoid carcinoma (EpCal), and a spontaneous mammary carcinoma (MaCal) were transplanted into adult thymectomized (TX) and/or sublethally irradiated (IRR, 560 R) mice at different intervals after irradiation. The primary response against SRBC was depressed in TX-IRR mice for up to three months after irradiation; in the IRR mice, the primary response was recovered by two months after irradiation. The secondary response slowly deteriorated with time after irradiation in the TX-IRR and IRR groups. The rejection time of skin grafts was significantly prolonged in both treatment groups at all time intervals, except in IRR mice transplanted one month after irradiation. MCG12 grew significantly more rapidly in female than in male mice except in TX-IRR mice transplanted at 1, 35, and 54 days, and in IRR mice transplanted at one day after irradiation. MaCal grew more rapidly in female than in male mice except for those TX-IRR mice transplanted at 1 and 35 days after irradiation. There was a significant increase in the incidence of lymph node metastases and lung metastases with MCG12 and EpCal, respectively. No increase in metastases was observed with MaCal. Thymectomy potentiated the increase in metastases in IRR mice, but only for a limited time (less than 35 days) after

irradiation. No relation was found between the effects of treatment on the growth and spread of tumors. The changes in tumor growth and spread varied with the tumor-host system, sex, and time of transplantation after irradiation. The authors conclude that the spread of weakly antigenic tumors can be influenced by immunosuppressive treatment.

- 5091 HETEROGENEITY OF PHAGOCYTTIC MALFUNCTION IN MYELOID LEUKAEMIA: LOCALIZATION OF THE PRIMARY DEFECT TO DECREASED INTRACELLULAR KILLING BY IMMATURE MYELOID CELLS. (Eng.) Koch, C. (Blegdamshospitalet, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark). *Acta Pathol. Microbiol. Scand.* [C] 83(5):383-389; 1975.

The capabilities of circulating WBC from seven patients with chronic myeloid leukemia (CML) and three patients with acute myeloblastic leukemia (AML) to ingest and to kill *Staphylococcus aureus* *in vitro* were investigated. Defects in both of these functions could be detected isolated or in combination. The most prominent finding was a highly significant correlation between decreased intracellular killing and degree of admixture of myelocytes and metamyelocytes to the mature cells. The data suggest that the main qualitative functional defect in CML as well as in AML is the inefficient intracellular killing capacity displayed by myelocytes and metamyelocytes. All but one of the patients were without signs of bacterial infection at the time of testing. The data thus add to the phenomena previously observed in this laboratory concerning the killing defect in severely infected patients, a defect which was found to be correlated in part with the degree of "shift to the left" of the myeloid cell population.

- 5092 VACCINATION AGAINST FELINE LEUKAEMIA VIRUS USING A CELL MEMBRANE ANTIGEN SYSTEM. (Eng.) Jarrett, W. (Leukaemia Res. Unit, Univ. Glasgow, Bearsden, Glasgow, Scotland); Jarrett, O.; Mackey, L.; Laird, H.; Hood, C.; Hay, D. *Int. J. Cancer* 16(1):134-141; 1975.

Cats inoculated with live feline lymphoblastoid cells of the FL74 line developed high titers of antibody to feline oncornavirus-associated cell membrane antigen (FOCMA). The level of response did not differ significantly in groups injected with FL74 cells in doses ranging from 10^6 to 10^8 /cat. Eight cats were subsequently challenged with a large dose of feline leukemia virus (FeLV) (10^7 IU) of a highly pathogenic strain. All resisted infection while 10 cats given the challenge virus alone became infected. The FeLV produced by FL74 cells was shown to be of extremely low infectivity in cats and in cultured feline cells. Cats inoculated with either FL74 cells or virus purified from them did not become infected. The purified virus did not induce FOCMA antibody in cats not previously exposed to FeLV. The fact that FL74 cells are highly immunogenic, but produce virus of low infectivity, is of value in devising vaccines against FeLV. Cats were also inoculated with FL74 cells which had been inactivated with paraformaldehyde. They developed FOCMA antibody,

reaching a peak titer of 256, and no virus could be cultured either from the vaccine preparations or from the tissues of the cats. The results demonstrate that vaccination of cats against FeLV is feasible.

- 5093 IMMUNOGLOBULINS AND ANTI-MAREK'S DISEASE VIRUS ANTIBODY SYNTHESIS IN CHICKENS AFTER PASSIVE IMMUNIZATION WITH IMMUNOGLOBULIN Y ANTI-MAREK'S DISEASE VIRUS ANTIBODY. (Eng.) Kermani-Arab, V. (College of Veterinary Medicine, Washington State Univ., Pullman, Wash. 99163); Moll, T.; Davis, W. C.; Cho, B. R.; Lu, Y. S.; Leslie, G. A. *Am. J. Vet. Res.* 36(11):1655-1658; 1975.

The effect of passive immunization with immunoglobulin Y (IgY) antibody against Marek's disease virus (MDV) was examined in MDV-susceptible White Leghorn cross chickens. The chickens were inoculated sc with 1500 plaque-forming U of MDV with or without sc administration of 27 mg IgY anti-MDV antibody on three successive days. Serum concentrations of IgM, IgY, and IgA were measured by radial immunodiffusion at intervals of 6-27 days after MDV exposure. The production of IgY, IgM, and probably also IgA was depressed in passively immunized chickens when compared with that in MDV-exposed chickens which had not been given IgY anti-MDV antibody. IgY concentrations in chickens treated only with MDV increased sharply at 17 days after inoculation, while IgY concentrations in passively immunized animals decreased beginning on day 9. IgM levels in both groups of chickens increased between days 9 and 14, but the increase was significantly higher in the chickens not inoculated with antibody. Untreated controls had no appreciable change in IgM concentration but showed a steady, slight increase in IgY concentration. In passively immunized chickens, the synthesis of IgM and IgY anti-MDV antibodies in responses to MDV infection was also delayed, as determined by agar gel precipitin and indirect fluorescence antibody tests. No synthesis of anti-MDV antibodies was observed in the controls. The depression of immunoglobulin production and anti-MDV antibody synthesis in passively immunized chickens suggests that the presence of passively administered antibodies may restrict MDV replication and dissemination, thus lowering humoral and cell-mediated immune responses.

- 5094 A UNIQUE COMPLEMENT DERIVED CHEMOTACTIC FACTOR FOR TUMOR CELLS. (Eng.) Romualdez, A. G., Jr. (Univ. Connecticut Health Center, Farmington, Conn.); Ward, P. A. *Proc. Natl. Acad. Sci. USA* 72(10):4128-4132; 1975.

A factor chemotactic for Walker carcinosarcoma and Novikoff hepatoma tumor cells could be generated by incubation of serum with an extract from tumor cells. A study was made to determine the nature of the factors in serum and tumor extract responsible for the chemotactic activity. The chemotactic behavior of WBC and tumor cells was assessed *in vitro* by the use of micropore filters, which separated two parts of a modified Boyden chamber. Cells tested for response were placed in the upper compartment, chemotactic test materials in the low-

er. The different tumor cells were obtained from peritoneal ascitic fluids, the WBC being removed from the tumor cells with the aid of a Ficoll-Hypaque gradient. The WBC used in the tests consisted of neutrophils obtained after ip instillation of glycogen. For quantitative assessment, cells that had moved through the filters were counted by light microscopy. Leukotactic factors which were tested included a culture filtrate of *Escherichia coli*, an homologous serum activated by incubation with zymosan, and preparations of third (C3) and fifth (C5) components of complement. Control experiments were carried out with B10-D2 mouse serum sufficient or deficient in C5 and with rabbit serum genetically devoid of C6. For suppression experiments, antibodies to C3 and C5 were raised in rabbits. Test extracts of the tumors were prepared by freeze-thawing procedures. Linear sucrose density gradients were used for preparation of fractions from tryptic digests of C5 to be tested for chemotactic activity. The chemotactic factor obtained by incubation of serum with tumor extract had no activity for neutrophilic leukocytes and the three preparations chemotactic for WBC were not chemotactic for tumor cells. Based on the results of further tests using complement deficient serums, purified complement components, antibodies against C3 and C5, tryptic digests of C3 and C5, and gradient fractions of trypsin-digested C5, the chemotactic factor for tumor cells was found to be a fragment of C5 and appeared to result from direct interaction of C5 with an enzyme in the tumor extract. Extracts from both Walker and Novikoff tumor cells generated chemotactic activity to which both cell types responded. The data indicate that chemotactic factors for tumor cells and neutrophils are different. It is suggested that if C5 plays a role in the development of metastatic lesions *in vivo*, the absence of C5 might be advantageous to the host; manipulative techniques designed to inhibit the activity of C5 fragments might impair the tendency of tumor cells to form metastatic foci.

- 5095 DETECTION OF A TL(+) MURINE LEUKEMIA CELL LINE THAT RESISTS THE CYTOTOXIC EFFECTS OF GUINEA PIG COMPLEMENT AND SPECIFIC ANTISERUM. (Eng.) Yu, A. (La Rabida Children's Hosp. and Res. Center, E. 65th St. at Lake Michigan, Chicago, Ill. 60649); Liang, W.; Cohen*, E. P. *J. Natl. Cancer Inst.* 55(2):299-308; 1975.

A study was carried out on the thymus-leukemia (TL) membrane-associated antigens of a radiation-induced leukemia (RADA-1) of mice. A spontaneously occurring leukemia (ASL-1) of phenotype TL 1,2,3, was also used in the study. Both tumors were maintained in strain A mice by ip transfer of spleen or ascites cells. TL 1,3; TL 1,2,3; TL 2; H-2^a; and H-2^b antisera were raised in appropriate allogeneic systems. Rabbit antiserum to normal mouse IgG (RAM) was also prepared. Reactivity of murine cells to specific antisera was determined by a guinea pig complement (C)-mediated cytotoxicity test and also by the use of fluorescein-conjugated RAM Ig. For tests on solubilized TL antigens, solubilization of ³H-fucose-labeled RADA-1 cells was accomplished with

Nonidet P40; the lysate supernatants were precipitated with specific alloantisera and RAM Ig; the precipitates were dissolved by boiling with 4% sodium dodecyl sulfate (SDS) and 1% 2-mercaptoethanol; and the final preparations were subjected to SDS-polyacrylamide gel electrophoresis. Adsorption tests were used to determine the quantity of specific membrane-associated TL antigens present on the RADA-1 cells. The RADA-1 cells (H-2^a thy-1b, TL 1,2,3) resisted lysis by C and TL 1,3 T 1,2 or TL 1,2,3 antisera. The cells expressed TL antigenic specificities as determined by fluorescence, direct isolation of TL antigen, and the capacity of the cells to reduce known titers of TL antisera. RADA-1 cells were not nonspecifically resistant to C-mediated lysis; they were killed in the presence of H-2^a antiserum and C. The TL antisera were shown to contain antibodies for TL determinants, since they stimulated the C-mediated lysis of ASL-1 cells and thymocytes from strain A mice (TL 1,2,3). It was concluded that the TL antigens of resistant RADA-1 cells had undergone antigenic modulation. After the cells were treated with neuraminidase, they became susceptible to the cytotoxic effects of aliquots of the same TL antisera and C used previously. The resistant RADA-1 cells expressed a lower concentration of antigens associated with their surface membranes than did the sensitive ASL-1 cells. This report was the first to indicate that modulation can proceed in cells which are resistant to lysis by TL antisera and C.

- 5096 EVIDENCE THAT BLOCKING FACTORS IN THE SERA OF MULTIPAROUS MICE ARE ASSOCIATED WITH IMMUNOGLOBULINS. (Eng.) Tamerius, J. (Univ. Washington Sch. Medicine, Seattle, Wash. 98195); Hellstrom, I.; Hellstrom, K. E. *Int. J. Cancer* 16:456-464; 1975.

Immunoabsorbents prepared from goat anti-mouse sera were used to investigate the nature of the blocking factors in the sera of multiparous BALB/c mice. A microcytotoxicity assay was used to measure the cell-mediated destruction of MCA 1315 of transplanted methylcholanthrene (MCA)-induced sarcoma target cells and its blocking by various sera. Immune lymph node cells (LNC) of BALB/c mice caused a reduction (28-51%) of target-cell numbers in the presence of 1:10 diluted normal serum. In the presence of multiparous serum, no significant cell-mediated immunity was detected. The average blocking activity (the ability of a test serum, in comparison with a control serum, to decrease cell-mediated destruction of target cells by immune LNC) in the six different pools of fractionated multiparous sera of 1:10-dilution was 99.7%. Adsorption of serum pool 4 to an anti-IgG₁, anti-IgG_{2a}, or anti-IgG_{2b} immunoabsorbent column reduced its blocking activity from 73 to 13%, 9%, and 12%, respectively. Elution of these columns permitted the recovery of 33%, 69%, and 87% of the blocking activity. The mean percentage reduction attained when multiparous LNC was used to measure blocking activity of each fraction was 36%. Adsorption of multiparous serum pools 3 and 4 to an anti-IgG₁ immunoabsorbent significantly reduced their blocking activities from 167 to 33%, and from 73 to 13%,

respectively. Blocking activity was recovered in the elution for these two pools. Adsorption of pools 1 and 6 had no effect on their blocking activities, nor was there any significant blocking activity demonstrated in their eluates. Adsorption of multiparous sera to either anti-IgG_{2a} or anti-IgG_{2b} immunoabsorbent reduced the blocking activities in every case. The blocking activities of these sera remained unchanged after adsorption to either anti-IgM or anti-IgA columns; no blocking activity was detected in their eluates. Passage of blocking serum through an immunoabsorbent coupled with antibodies from a rabbit anti-mouse serum removed all of its blocking activity, and this could be recovered in the eluates. The authors suggest that the blocking factors in this system are largely complexes between embryonic antigens and IgG_{2a} and IgG_{2b}.

- 5097 REGION OF IMMUNOGLOBULIN LIGHT-CHAIN mRNA TRANSCRIBED INTO COMPLEMENTARY DNA BY RNA-DEPENDENT DNA POLYMERASE OF AVIAN MYELOBLASTOSIS VIRUS. (Eng.) Schechter, I. (Weizmann Inst. of Science, Rehovot, Israel). *Proc. Natl. Acad. Sci. USA* 72(7):2511-2514; 1975.

The enzymic synthesis and characterization of the DNA complementary to highly purified messenger RNAs (mRNA) coding for M-321, M-63, M-41, and M-104E L chains from mouse myeloma polysomes is described. Thirty percent of the M-321p mRNA was reverse transcribed to complementary DNA (cDNA) when presented with the avian myeloblastosis virus DNA polymerase. The cDNA hybridized with the M-321p mRNA with the product of RNA concentration (M/L) and time in seconds ($C_{rt}_{1/2}$) being 6×10^{-4} ; at saturations 65% of the cDNA was annealed. The hybrids showed a biphasic thermal denaturation curve. High ($T_m = 95^\circ\text{F}$) and low ($T_m = -86^\circ\text{F}$) melting temperature (T_m) fractions of melted hybrids were resolved by hydroxylapatite columns; high T_m cDNA and M-321 mRNA hybridized, with a $C_{rt}_{1/2}$ of 2.6×10^{-4} . At saturation, 97% of the cDNA was annealed. The hybrids consisted of well-matched duplexes, because they had a high T_m (89 F) with a sharp denaturation profile. A value of 8S, corresponding to a molecular weight of 280,000 (840 nucleotides), was obtained when the cDNA was sized on an alkaline sucrose gradient and determined by the extent of protection of mRNA from ribonuclease digestion. The cDNA annealed with κ -type L-chains. The values of cDNA hybridized at saturation with various κ -type cDNA was used to quantify the mRNAs coding for all κ -type L-chains. The values of cDNA hybridized at saturation with various κ -type mRNAs indicate that (a) the cDNA is complementary to the entire constant region and to about half of the variable (V) region (b) V regions of similar amino acid sequence are coded by a similar nucleotide sequence; and (c) the nucleic acid probe to one V region may anneal and quantify V region genes of members of the same group.

- 5098 TYPE SPECIFICITY OF COMPLEMENT-REQUIRED AND IMMUNOGLOBULIN M NEUTRALIZING ANTIBODY IN INITIAL HERPES SIMPLEX VIRUS INFECTIONS OF HUMANS. (Eng.) Schmidt, N. J. (Viral and Rickettsial Disease Lab., California State Dept.

Health, Berkeley, Calif. 94704); Forghani, B.; Lennette, E. H. *Infect. Immun.* 12(4):728-732; 1975.

A study was carried out on the type specificity of the immunoglobulin M (IgM)-neutralizing antibody produced in initial herpes simplex virus (HSV) type 1 and type 2 infections and on the enhancing effect of guinea pig complement on homotypic and heterotypic IgM and immunoglobulin G (IgG) neutralizing antibodies elicited by initial HSV infections. The use of a highly sensitive and specific solid-phase radioimmunoassay for typing HSV antibody permitted accurate determination of patients' current infecting virus type and indicated whether the patients had previously experienced an infection with the HSV heterotype. The method was based on absorbing sera with cells infected with HSV-1 or HSV-2 and testing for residual antibody. Sera were titrated by a plaque reduction neutralization test, using MacIntyre strain HSV-1 and Johnson strain HSV-2. Parallel tests were carried out in the presence and absence of complement. Sucrose density gradient centrifugation was used for separation of IgM and IgG antibodies, and their specificity and purity were determined by double immunodiffusion tests against gamma-chain-specific anti-human IgG and mu-chain-specific anti-human IgM. Sera were taken from 15 patients who were apparently experiencing an initial infection with HSV and from six patients with a history of recurrent HSV infection and showing only HSV-1 antibody in their sera. It was found that antibodies to HSV-1 and HSV-2 in initial HSV infections of humans were enhanced by complement to about the same extent, and there was no significant difference in the degree to which complement enhanced homotypic and heterotypic HSV-neutralizing antibody. Homotypic and heterotypic IgG neutralizing antibodies were enhanced by complement to as great, or greater, an extent than the corresponding IgM antibodies in the same sera. In patients with initial HSV-1 infections, the IgM neutralizing antibody response was type specific. On the other hand, patients with initial HSV-2 infections produced both homotypic and heterotypic IgM neutralizing antibody. An initial HSV-2 infection in an individual previously infected with HSV-1 elicited the production of IgM neutralizing antibody to both HSV-1 and HSV-2. However, patients with recurrent infections failed to produce IgM antibody to either HSV type during reactivation of the virus.

5099 A SEARCH FOR ANTIBODIES AGAINST HUMAN SARCOMA CELLS IN PATIENTS' SERA BY INDIRECT IMMUNOFLUORESCENCE ON FIXED CELLS. (Eng.) Laprevotte, I. (Hôpital Saint-Louis, 2, place du Docteur-Fournier, 75010 Paris, France); Chuat, J. C.; L'Hirondel, A. M.; Bernard, C.; Peries, J.; Boiron, M. *Eur. J. Cancer* 11(10):757-762; 1975.

Fourteen human sarcomas (osteosarcomas, soft tissue and reticulum cell sarcomas), were examined by an indirect immunofluorescence technique for antibodies against human sarcoma. This report is part of an exhaustive study in which cytology, cellular proliferation, karyologic studies, electron microscopy, virology and immunology are combined. The antigens were prepared by biopsy im-

prints, cell smears of disrupted tissues, cell smears of tissue cultures, cells grown on slides, and tumor cells cocultivated with calf skin cells. Control tumors consisted of two benign tumors. Nineteen patients affected by a variety of sarcomas were used as test sera. The antigen preparations were in most cases reacted with dilutions of test serum (undiluted, 1:2, 1:5, 1:10, 1:50, and 1:100) at 37 C for 45 min and reacted with dilutions of antihuman globulin goat globulin-fluorescein conjugate. A total of 427 tests were performed and all were negative. The authors reason that the diverse antigens and techniques may be the cause for the discrepancies between the results of this work and those reported previously by others.

5100 CLINICAL AND IMMUNOLOGICAL SIGNIFICANCE OF HUMAN MELANOMA CYTOTOXIC ANTIBODY.

(Eng.) Bodurtha, A. J. (Inst. Cancer Res., Fox Chase Center, Philadelphia, Pa. 19111); Chee, D. O.; Laucius, M. J.; Mastrangelo, M. J.; Prehn, R. T. *Cancer Res.* 35(1):189-193; 1975.

The activity of complement-dependent cytotoxic serum antibody in 21 patients with malignant melanoma was investigated with a microtoxicity assay. Correlation with the presence of antibody was sought for clinical stage of the disease, tumor burden size, reactivity of immune system, and therapy response. Heat-inactivated sera reacted against mechanically dispersed fresh tumor cells in the presence of exogenous blood group AB Rh-positive complement. Cytotoxicity was evaluated against a pooled normal serum control. Sera were cytotoxic against antibody-positive tumor cells in 9 of 10 patients with regional melanoma and in 1 of 11 patients with disseminated metastases. Six of seven cases of antibody toxic sera were noncytotoxic to 2-7 different allogeneic melanoma tumor cell preparations. Cytotoxic antibody-positive and -negative groups were similar in their capacity to be sensitized to dinitrochlorobenzene, to produce positive skin tests to microbial antigens, and to produce antibodies to typhoid vaccination. Serum immunoglobulins were present. Thus, the presence of cytotoxic antibody allowed the prediction of the response to immunotherapy. There was a greater survival rate in the cytotoxic antibody-positive patients. The presence of the antibody was related to the clinical stage of the disease and not to the tumor burden size. This supports the findings of the presence of cytotoxic antibody in the sera of melanoma patients without disseminated metastases.

5101 DETECTION IN COLORECTAL CARCINOMA PATIENTS OF ANTIBODY CYTOTOXIC TO ESTABLISHED CELL STRAINS DERIVED FROM CARCINOMA OF THE HUMAN COLON AND RECTUM. (Eng.) Schultz, R. M. (Natl. Cancer Inst., Bethesda, Md. 20014); Woods, W. A.; Chirigos, M. A. *Int. J. Cancer* 16(1):16-23; 1975.

Studies were performed of the humoral cytotoxic responses of patients with carcinomas of the lower intestine to antigens found on established cell strains derived from carcinomas of the human colon and rectum. Sera from eight of 15 patients with colonic carcinoma exhibited demonstrable cytotoxicity against an established cell strain derived from

adenocarcinoma of the ileocecum, HCT-8. Sera from 12 of 16 patients with rectal carcinoma were cytotoxic for an established cell strain derived from an adenocarcinoma of the rectum, HRT-18. Patients with colonic carcinoma exhibited serum cytotoxicity against only the colonic target cells, whereas patients with rectal carcinoma gave significant cytotoxicity against both cell strains. This cytotoxicity was shown to be complement-dependent and appeared to be specific for colonic and/or rectal carcinoma cells. Although the cells produced carcinoembryonic antigen (CEA) *in vitro*, the cytotoxic antibody response in these patients did not appear to be directed against CEA. Serum cytotoxicity was not demonstrated against two other cell strains, HCT-48 and HT-29, derived from adenocarcinomas of the human colon, except for a reaction against a blood-group-related antigen. These cell strains had comparable levels of cell-associated CEA. The routine titration of cytotoxic antibody against these established cell cultures may provide meaningful information on the host's immune response to colorectal neoplasms.

- 5102 CARCINOEMBRYONIC ANTIGEN AND HUMORAL ANTIBODY RESPONSE IN PATIENTS WITH THYROID CARCINOMA. (Eng.) Rochman, H. (Dept. Pathology and Medicine, Univ. Chicago, Chicago, Ill. 60637); deGroot, L. J.; Rieger, C. H. L.; Varnavides, L. A.; Refetoff, S.; Joung, J. I.; Hoyer, K. *Cancer Res.* 35(10):2689-2692; 1975.

The relationship between carcinoembryonic antigen (CEA) and humoral antibody response in patients with thyroid carcinoma and previous irradiation to the thymus or tonsils was studied in 237 patients and 129 controls. Of the 237 patients, 57 had thyroid cancer of whom 26 had no history of prior irradiation and their mean age was 38.4 yr. The remaining 31 cancer patients had a prior history of irradiation and their mean age was 30.7 yr. One hundred eighty patients, additionally, had positive histories of irradiation. The procedure for measuring CEA was that of Lawrence; thyroglobulin and microsomal antibody titers were also measured. For CEA, levels greater than 12.5 ng/ml were abnormal and for antibodies, a dilution of 1:20 or greater was positive. Elevated levels of CEA were found in 24% of noncancer patients with histories of thymic or tonsillar irradiation vs 10% for controls. In the thyroid cancer group 36% had elevated CEA levels and of these patients 18% had prior irradiation while 56% did not. Notably, in this latter group CEA levels tended to be markedly increased (over 20 ng/ml). Thyroglobulin antibodies were detected in 3% of controls, 8% of noncancer patients with prior irradiation, and 14% of cancer patients. Microsomal antibody levels were positive in 10% of controls, 17% of noncancer-irradiated patients, and 22% of thyroid cancer patients. The finding of increased CEA levels in thyroid cancer patients without previous irradiation corroborates other reports, both human and animal. There was no evidence of an association between CEA levels and tumor differentiation, or age. It is suggested that antigenic expression and host response to the tumor

in patients with thyroid cancer depends on its pathogenesis.

- 5103 DETECTION OF CARCINOEMBRYONIC ANTIGEN IN TISSUE SECTIONS BY IMMUNOPEROXIDASE. (Eng.) Primus, F. J. (Univ. Kentucky Medical Center, Lexington, Ky. 40506); Wang, R. H.; Sharkey, R. M.; Goldenberg, D. M. *J. Immunol. Methods* 8(3):267-275; 1975.

A triple-bridge, indirect, immunoperoxidase method for detecting and localizing carcinoembryonic antigen (CEA) in tissue sections is described. The method involves the binding of goat anti-CEA antibody to the antigen-containing tissue. Rabbit anti-goat IgG is bound to the previous antibody; and goat anti-peroxidase is then also bound to the rabbit anti-goat IgG antibody. By this technique, a cell-surface localization of CEA in colonic carcinoma and ovarian mucinous cystadenocarcinoma cells could be visualized. In the case of the colonic cancer, both the tumor from the descending colon and a metastasis to the skin gave positive peroxidase reactions for CEA. This immunocytochemical method for demonstrating the presence of CEA functioned in both frozen, ethanol-fixed and formalin-fixed, paraffin-embedded tissues, thus making it applicable for use with tissue sections conventionally prepared for light microscopy.

- 5104 CARCINOEMBRYONIC ANTIGEN IN AN UNSELECTED ELDERLY POPULATION: A FOUR YEAR FOLLOW UP. (Eng.) Stevens, D. P. (Royal Melbourne Hosp., Victoria 3050, Australia); Mackay*, I. R.; Cullen, K. J. *Br. J. Cancer* 32(2):147-151; 1975.

Sera obtained in 1969 from 956 unselected elderly (at least 60-yr-old; 73 older than 80 yr) persons in Busselton, Western Australia were tested for carcinoembryonic antigen (CEA) by a "double antibody" microradioimmunoassay. Forty-four (4.5%) were positive for CEA (5 ng/ml or greater). No special investigations to demonstrate CEA-related diseases were done. The results of the CEA tests were not known to the subjects' local practitioners. Review of health records for the 4-year period subsequent to accession of sera showed that 6 (14%) of the 44 persons positive for CEA died of CEA-associated cancers, 15 were heavy smokers, two had colonic diverticula and one a peptic ulcer. On the other hand, 18 (2%) of the 912 persons negative for CEA developed CEA associated cancers. Thus, a significantly greater proportion of cancers ($P=0.01$) was found in the persons positive for CEA. Furthermore, when 21 persons who were positive for CEA in 1969, but clinically well four years later, were examined, two had occult cancer of lung and colon respectively. In 20 subjects there was no discernible cause for the positive CEA test result. However, the relatively low yield of diagnosis of cancer from our present population survey led to the conclusion that, if screening for cancer were to be solely dependent on testing for CEA, increased specificity and sensitivity of test systems should be awaited.

- 5105 MOUSE T-CELL SURFACE GLYCOPROTEIN RECOGNIZED BY HETEROLOGOUS ANTI-THYMOCYTE SERA AND ITS RELATIONSHIP TO THY-1 ANTIGEN. (Eng.) Trowbridge, I. S. (Salk Inst. for Biological Studies, PO Box 1809, San Diego, Calif. 92112); Weissman, I. L.; Bevan, M. J. *Nature* 256(5519):652-654; 1975.

A mouse T cell surface glycoprotein (T25) of low molecular weight is described. The molecule, recognized by immunoprecipitation studies of labeled thymocytes and both absorbed and unabsorbed anti-mouse thymocyte serum (ATS), is present on mouse thymocytes, T lymphomas, and peripheral T cells. It is also recognizable by rabbit antisera that express the Thy-1 antigen to mouse lymphocytes. T25 cannot be detected on the surface of Thy-1-negative mouse T lymphoma cell lines. The amount of radioactivity associated with T25 suggests that it is a major component of the thymocyte cell surface. The recognition of T25 by an antiserum specific for Thy-1 alloantigenic determinants suggests that T25 is identical with Thy-1 antigen. Therefore, the authors recommend that earlier reports that suggest that mouse Thy-1 antigen is a glycoprotein should be re-examined.

- 5106 α -FETOPROTEIN AND HEPATITIS B ANTIGEN IN HEPATOMA AND HEPATITIS. (Eng.) Ichida, F. (Dept. Internal Medicine, Faculty of Medicine, Niigata Univ., Niigata, Japan); Shibasaki, K. *Ann. N.Y. Acad. Sci.* 259:259-260; 1975.

The relationship between α -fetoprotein (AFP) hepatitis B antigen (HBsAg), and hepatic cirrhosis in hepatoma, and in acute viral hepatitis was studied. The radioimmunoassay was considered positive at AFP > 20 ng/ml. In 60 of 63 cases of hepatomas, AFP was found. The maximum level was > 300 mg/dl. In 12 of 33 cases of acute viral hepatitis, 9 of 19 cases of chronic hepatitis, and 17 of 44 cases of hepatic cirrhosis, AFP was found. It was also detected in 7 of 39 cases of metastatic liver cancer. A case of acute viral hepatitis with a transient high (9750 ng/ml) AFP level is described. The peaks of AFP in this and two other cases suggest that a high titer of AFP corresponds to the presence of zonal necrosis.

- 5107 ANALYSIS OF SOLUBLE MELANOMA CELL MEMBRANE ANTIGENS IN METASTATIC CELLS OF VARIOUS ORGANS AND FURTHER STUDIES OF ANTIGENS PRESENT IN PRIMARY MELANOMA. (Eng.) Hollinshead, A. C. (The George Washington Univ., Dept. Medicine, Ross Hall, Room 526, 2300 I St., NW, Washington D.C. 20037). *Cancer* 36(4):1282-1288; 1975.

Sephadex G-200 chromatography and polyacrylamide gel electrophoresis (PAGE) were employed to analyze the soluble melanoma cell membrane antigens in melanoma metastases of the liver, lung, adrenals, skin, colon, a series of six skin lesions from one patient collected over a 2-mo period, and 19 skin lesions of another patient collected over a 2.5-mo period. In addition, a study was conducted to determine whether skin-reactive melanoma antigens could be prepared from large metastatic deposits. The best total recovery of soluble antigen was from the skin (48%) and colon metastatic (40%) tissues; good yields

were also obtained from liver (34%), lung (32%), and one of the pools of skin lesions (37%). The tumor-associated melanoma antigen found in Sephadex fraction II and PAGE region a was strongest in the adrenal, lung, and liver metastases demonstrating that the protein yield in PAGE region a was not indicative of the strength of the antigen. Therefore, a careful, detailed analysis of the protein bands in the PAGE regions a and b (bands a₁-a₃ through b₁-b₇) from primary skin melanomas was then conducted to determine which band was related to skin-reactive antigenic activity. Only one band, a₁, a glycolipoprotein, was responsible for positive skin reactivity. In additional studies to determine whether some of the antigens present might also be fetal antigens, some of the melanoma protein bands of Sephadex fraction III and PAGE region b appeared similar to PAGE region b proteins of fetal skin cells. Two bands from fetal skin also had the same location on PAGE as two bands from ductal breast cancer cell membranes; the relation to melanoma region b was not exact. The authors suggest that these fetal proteins, present on both ductal breast cancer and melanoma cell membranes, might account for the positive skin reactivity of this region.

- 5108 SPECIFICITY OF CELL MEMBRANE ANTIGENS IN PROSTATIC CANCER. (Eng.) Brannen, G. E. (Johns Hopkins Hosp., Baltimore, Md. 21205); Gomolka, D. M.; Coffey, D. S. *Cancer Chemother. Rep. (Part I)* 59(1):127-138; 1975.

(BALB/c x DBA₂)F₁ hybrid mice bearing a 3-methylcholanthrene-induced fibrosarcoma (MCAM-7) transplant in the right leg underwent surgical excision of the tumor and showed specific resistance to subsequent challenges with that identical tumor line. An *in vivo* response to tumor-specific antigens (MCAM-7 antigen) solubilized by hypertonic potassium chloride was measured by 24-hr footpad swelling response in mice immunized to the tumor from which the antigens were extracted. These observations suggested that the transplantable MCAM-7 fibrosarcoma could produce immunity toward the solubilized MCAM-7 tumor antigens and that this tumor immunity could be measured by footpad swelling response to injection of the solubilized antigens, an indication of cell-mediated immunity. The footpad swelling response was also monitored in relation to the extent of tumor growth. Mice received MCAM-7 tumor transplants by injection of 5 x 10⁶ tumor cells and were tested for footpad swelling response at intervals following tumor transfer. A significant footpad response to injected MCAM-7 antigens was present 10 days following tumor transfer; at this time signs of tumor growth were only minimally detectable. The footpad swelling response to injected antigens disappeared by 28 days following initial tumor transfer; at this time the tumor diameters were in excess of 1.0 cm. Surgical removal of tumor at this point promptly restored footpad responses within 24 hr. Similar techniques have been applied to patients bearing adenocarcinoma of the prostate, where skin testing was substituted for the measurement of footpad swelling in animals. Seven patients with known prostatic carcinoma were given intradermal injections of soluble tumor antigens extracted from

their own tumors. Three of the seven patients exhibited a cutaneous delayed type hypersensitivity response to the injected autologous tumor extracts. No positive reactions were observed in response to solubilized components of control tissues, including benign prostatic hyperplasia. The significance of the demonstrated concomitant immunity in these patients has not been resolved. However, these observations suggest that some patients bearing adenocarcinoma of the prostate can exhibit an immunologic response to specific antigens present in their own neoplasms.

- 5109 TUMOR ANTIGEN AND ACID PHOSPHATASE ISOENZYME IN PROSTATIC CANCER. (Eng.) Chu, T. M. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14203); Bhargava, A.; Barnard, E. A.; Ostrowski, W.; Varkarakis, M. J.; Merrin, C.; Murphy, G. P. *Cancer Chemother. Rep. (Part 1)* 59(1):97-103; 1975.

Plasma and prostatic fluid from man, dog, and baboon were measured for carcinoembryonic antigen (CEA) by a radioimmunoassay technique. No CEA was detected in plasma, prostatic fluid, or seminal fluid in 12 dogs and three baboons. Elevated CEA (> 2.5 ng/ml) was found in 13 of 20 human prostatic fluids. It was inferred that there was no immunologic cross-reactivity of CEA among man, dog, and baboon. CEA has been isolated and purified from liver tumors. Biochemical studies revealed that CEA consists of 60% carbohydrate and 40% protein. It contains the following carbohydrates: fucose, mannose, galactose, sialic acid, N-acetylglucosamine, and a small amount of N-acetylgalactosamine. The following amino acids were found in CEA: lysine, histidine, arginine, aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, and cysteine. The amino acid sequence (first 30 amino acids) of the N-terminal has been determined. The N-terminal amino acid was lysine. Using this study as a model, other tumor antigens from prostatic tumor tissues are being investigated. The acid phosphatase isoenzyme from prostatic tissue was also studied. After a series of purifications, two chromatographic fractions were obtained. Treatment with neuraminidase removed the sialic acid content of the molecule, changed the isoelectric focusing patterns, and abolished the chromatographic heterogeneity. Sedimentation studies indicated a molecular wt of about 100,000. Biochemical studies showed that prostatic acid phosphatase isoenzyme is a glycoprotein which consists of 7% carbohydrate and 93% protein. It contains fucose, galactose, mannose, sialic acid, N-acetylglucosamine, and the following amino acids: aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, lysine, histidine, arginine, tryptophan, and cysteine. An antiserum to this purified prostatic acid phosphatase isoenzyme is being prepared in animals.

- 5110 IMMUNE RESPONSES TO SOLUBLE TUMOR ANTIGENS IN VARIOUS STAGES OF TUMOR GROWTH. (Eng.) Brannen, G. E. (Johns Hopkins Hosp., Baltimore, Md.

21205); Santos, G. W. *Invest. Urol.* 13(2):79-84; 1975.

The usefulness of soluble tumor-specific antigens of 3-methylcholanthrene (MCA)-induced murine fibrosarcomas as footpad test antigens for monitoring immunologic reactions to syngeneic tumors was tested in male (BALB/c x DBA/2) F₁ hybrid mice. Nine mice were injected sc with 2 mg MCA. The resulting tumors were excised, suspended, and injected into footpads of another group of mice (5×10^6 cells). When these tumors reached 0.5-1.0 cm diameter, they were excised; one week later experimental and control mice were challenged in the remaining footpads with graded doses of tumor cells to test for transplantation immunity. An *in vivo* response to tumor-specific antigens solubilized by hypertonic potassium chloride was measured by 24-hr footpad swelling response in mice immunized to the tumor from which the antigens were extracted. Normal mice given an injection of 5×10^6 tumor cells showed significant 24-hr footpad swelling response to solubilized tumor antigens (solubilized from the tumor line injected) ten days after tumor transfer. The responses were negative 28 days after tumor transfer, when tumor diameters were in excess of 1.0 cm. Surgical removal of tumor at this point promptly restored footpad responses within 24 hr. Continued study of this response correlated with other measures of *in vitro* with *in vivo* tumor immunity holds promise not only of understanding the nature of the footpad response itself, but also of unraveling some of the immunologic mechanisms of host-tumor interactions.

- 5111 LYMPHOCYTE RESPONSES OF LUNG CANCER PATIENTS TO TUMOR-ASSOCIATED ANTIGEN MEASURED BY LEUCINE INCORPORATION. (Eng.) Roth, J. A. (Sepulveda Veterans Administration Hosp., Los Angeles, Calif.); Holmes, E. C.; Boddie, A. W., Jr.; Morton, D. L. *J. Thorac. Cardiovasc. Surg.* 70(4):613-618; 1975.

Lymphocyte responses to lung carcinoma-associated antigens were assessed by measuring ³H-leucine incorporation in lymphocytes from 20 lung cancer patients, from 37 patients with other neoplasms, and from 20 normal subjects. Antigens were prepared from nine lung carcinomas by extraction with 3M KCl. Fifteen of 20 lung cancer patients showed increased leucine incorporation to one or more tumor antigens, whereas only 5 of 20 normal subjects responded ($P < 0.005$). Lymphocyte responses to both autologous and allogeneic tumor extracts were observed. Lymphocytes from eighteen lung cancer patients were tested with the most reactive antigen and 13 responded. Lymphocytes from seven of 37 patients with other neoplasms and 2 of 18 normal subjects reacted to this antigen. Lymphocytes from significantly more lung cancer patients reacted to the tumor extract than to an extract of uninvolved lung from the same patient. The reactivity of lymphocytes from lung cancer patients clinically free of disease was significantly greater than that of patients with disseminated disease. Extraction of lung carcinomas with 3M KCl is a useful technique for solubilizing tumor-associated antigens (TAA).

Antigenic activity may be followed *in vitro* by measuring lymphocyte ^3H -leucine incorporation.

- 5112 ABSENCE OF H-2 ANTIGENS CAPABLE OF RE-ACTING WITH CYTOTOXIC T CELLS ON A TERA-TOMA LINE EXPRESSING A T/t LOCUS ANTIGEN. (Eng.) Forman, J. (Univ. Texas Southwestern Medical Sch., Dallas, Tex. 75235); Vitetta, E. S. *Proc. Natl. Acad. Sci. USA* 72(9):3661-3665; 1975.

The capacity of F9 cells in cell-mediated lympholysis (CML) assay to act as target cells for cytotoxic T cells that have been sensitized to H-2 antigens of 129 strain cells was investigated. Irradiated C57BL/10Sn (H-2^b) or 129/J (H-2^{b/c}) spleen cells were cocultured with H-2 allogeneic responders to generate cytotoxic T (effector) cells. The effector cells displayed a specific cytotoxic effect against lymphoblasts from strain 129 (10.7% net ^{51}Cr release), but against F9 target cells no increase in percent isotope release was observed (-7.2%). It has been observed previously that modification of spleen cells with reactive haptens allows them to sensitize syngeneic cells so as to induce cytotoxic T cells specific for the syngeneic haptenated targets. Furthermore, the specificity of the response is dependent on the H-2 genotype of the target cell; i.e., hapten-modified targets from an unrelated H-2 haplotype to the sensitizing strain are not killed. If the specificity of these effector cells is directed against new determinants created on a given H-2 glycoprotein by the haptenation procedure, then one may be able to detect such determinants on F9 cells. Spleen cells from 129 strains respond to trinitrophenyl-modified 129 stimulators by inducing lysis of trinitrophenyl-modified targets. However, the same effector cells did not cause significant lysis against trinitrophenyl-modified F9 target cells. Furthermore, with haptenated F9 cells as stimulators, no significant lysis was observed against haptenated F9 targets. Thus, the F9 antigen is structurally similar to H-2^b, but does not act as a target antigen in the cell-mediated lympholysis assay for anti H-2^b cytotoxic T cells, nor does it cross react with H-2^b antigens at the T cell level.

- 5113 BINDING OF α -FETOPROTEIN TO MURINE T CELLS. (Eng.) Dattwyler, R. J. (Mayo Medical Sch., Rochester, Minn. 55901); Murgita, R. A.; Tomasi, T. B., Jr. *Nature* 256(5519):656-657; 1975.

The cell types affected by α -fetoprotein (AFP) were determined by studying the binding of (AFP) to the surface of various cells involved in the immune reaction. Preparations of thymus-derived lymphocytes (T cells), bone marrow-derived lymphocytes (B cells), and macrophages from 6- to 10-wk-old female C57BL mice were examined by direct immunofluorescence. AFP was isolated from the amniotic fluid of Ha/ICR mice during the late second trimester of pregnancy. Spleen cells were treated with either anti-Fab or anti-plus complement, and then passed sequentially over glass and nylon wool columns. AFP bound to the T cells (18%) that were not adherent to nylon wool were destroyed by anti-plus complement. No binding was

observed with B-cell enriched populations (spleen treated with anti-plus complement) or in the spleens of nude mice. Approximately one-third of the T cells bound to AFP, suggesting that a subclass of T cells may be involved in AFP suppression. A relatively small number of thymocytes (less than 1%) and cortisone-resistant thymus cells (6%) bound to AFP suggesting AFP binding involves the detection of surface receptors which require additional maturation after peripheralization from the thymus. The results demonstrate that antisera, spleen, lymph node, and cortisone-resistant thymocytes (but not bone marrow or nude mouse spleen cells) contain AFP binding cells.

- 5114 SCANNING ELECTRON MICROSCOPY OF NORMAL AND MITOGEN-STIMULATED MOUSE LYMPHOID CELLS. (Eng.) Criswell, B. S. (Baylor Coll. Medicine, Houston, Tex. 77025); Rich, R. R.; Dardano, J.; Kimzey, S. L. *Cell Immunol.* 19(2):336-348; 1975.

Surfaces of normal, cultured, and mitogen-stimulated mouse lymphoid cells were examined by scanning electron microscopy (SEM). Lymphocytes with smooth, highly villous and intermediate surfaces were observed in cell suspensions from both spleens and thymuses of normal mice (BALB/c, A/Tex, C57BL/6, and C3H/He) and from spleens of congenitally athymic (nude) mice. Several strain-specific surface features were noted, the most striking of which was the spine-like appearance of microvilli on C57BL/6 lymphocytes. Although thymus cell suspensions contained somewhat more smooth cells than did spleen cell preparations, lymphocyte derivation could not be inferred from SEM examination. Studies of cells stimulated with agents mitogenic for thymus-derived lymphocytes (concanavalin A, 1 $\mu\text{g}/\text{ml}$) or for bone-marrow-derived lymphocytes (lipopolysaccharide) showed an increase in the number of villous cells. This increase was most distinct at 24-48 hr of culture with mitogen; an increase from 2% villous cells with no mitogen to 46% villous cells occurred after 48 hr with lipopolysaccharide, an increase from 6% villous cells to 48% after 48 hr occurred with concanavalin A. This suggests that development of a complex villous surface in the mouse is a general concomitant of lymphocyte activation and transformation.

- 5115 FINE STRUCTURAL STUDY ON HUMAN T- AND B-LYMPHOCYTES. (Jpn.) Watanabe, Y. (Sch. Medicine, Keio Univ., Tokyo, Japan); Tamaoki, N.; Habu, S.; Tashiro, Y.; Akatsuka, S.; Enomoto, Y. *Acta Haematol. Jpn.* 37(5):655-666; 1974.

Human lymphocytes from peripheral blood were studied in serial sections under an electron microscope. A characteristic cytoplasmic structure, which consisted of several small dense bodies clustered in a restricted area of the cytoplasm, was found in some of lymphocytes and was tentatively designated as "clustered dense bodies" (CDB) in contrast to usual dense bodies scattered in the cytoplasm (scattered dense bodies, SDB). Lymphocytes forming rosettes with SRBC (E) and those forming rosettes with complement-coated SRBC (EAC) were studied in serial sections. Forty six cells from E- and 33 cells from EAC-rosetting lymphocytes, all of which

were sectioned serially over at least 1/3 of the diameter of cells, were observed. Clustered dense bodies and Gall bodies, each of which was present singularly in a given lymphocyte, were found more frequently in E-rosetting lymphocytes than in EAC-rosetting ones, whereas SDB and cytoplasmic processes were found more frequently in EAC-rosetting lymphocytes. The difference was highly significant. This indicates that CDB and Gall body can serve as morphological markers for T-cells, and SDB and cytoplasmic processes for B-cells. Among these four structures, CDB seemed to be most reliable as a morphological T-cell marker. Contact area between lymphocytes and SRBC was measured in E- and EAC-rosetting lymphocytes. Contact area was distinctly smaller in E-rosetting cells (less than 2% of the total surface area) than in EAC-rosetting cells in which the contact area exceeded 2% of the total surface area in more than 60% of cells observed. This indicates that the receptor sites to E in T-cells are less numerous than the receptor sites to the complement in B-cells. When present in EAC-rosetting lymphocytes, CDB were always seen in those with scanty contact area.

- 5116 THE FINE STRUCTURE OF THE LYMPHOCYTE NUCLEUS UNDER CONDITIONS OF PHYTOHAEMAGGLUTININ STIMULATION. (Eng.) Valkov, I. (Acad. Medicine, 1, Georgi Sofiiski Str., Sofia 31/ Bulgaria). *Acta Neuropathol.* [Suppl.] (Berl.) 6:57-63; 1975.

The nucleus of phytohemagglutinin (PHA)-cultured lymphocytes was studied by EDTA, Thallium-Schiff and uranyl-lead techniques. Guinea pig lymph node lymphocytes were cultivated for 1-6 hr and 24 and 48 hr with PHA. A morphometric study was performed on electron micrographs of EDTA-treated material. Specimens of the thymus and of the bursa of Fabricius of newborn chickens were also studied in this manner. Scattering of the dense chromatin, increase in the number of nuclear bodies and nucleolar modifications were established. Transportation was seen of granules similar to perichromatin ones from the nucleus into the cytoplasm. Morphometric investigation revealed a decrease between 7.7-26.3% of the dense chromatin also that the number of perichromatin granules was the greatest in the untransformed PHA lymphocytes (e.g. B lymphocytes). The lymphocytes of the bursa of newborn chickens contained more perichromatin granules per unit area of nuclear surface (1.848) and dense chromatin surface (35.5) than did the lymphocytes of the thymus (0.883 and 58.4 for nuclear surface and dense chromatin, respectively). This suggests the ability of whole perichromatin granules to pass into the cytoplasm.

- 5117 PHYSIOLOGICAL SIGNIFICANCE OF THE LYMPHOCYTIC CELL COAT. (Eng.) Bona, C. (Immunotherapie Experimentale, C.N.R.S., Paris). *Biomedicine* 22(2):97-104; 1975.

Relationships are described between chemical and physical characteristics of cell coats of lymphocytes and the physiological properties of the cells. Lymphocyte membranes coated by a glycoprotein layer consisting of a single polypeptide chain extending into the cytoplasm of the cell. The oligosaccharide ex-

posed to the external environment of the cell and the C-terminal portion anchored to the cytoplasm are linked by an intermediary portion rich in nonpolar and hydrophobic amino acids which seems to represent the region of the molecule that spans the lipid bilayer of the membrane. High magnification photographs show a thicker coat on T-cells than on B-cells and colloidal lanthanum staining studies give negative results for thymocytes, 30% positive results for lymph node lymphocytes, and 100% positive results for bone marrow lymphocytes. Modulation of the cell coat during blast formation is shown by the observation that capping of lymphocytes induced by phytohemagglutinin is paralleled with an accumulation of granular particles in the zone of the membrane which was capped by the mitogen. Since the electrophoretic mobility of cells is due to electronegative charges carried by the glycoproteins of the cell coat, sialidase and sulfatase treatments of guinea pig lymphocytes results in marked decreases of mobility, while no change is observed following treatment with β -glucosidase, α -maltase, β -galactosidase and lecithinase. B- and T-derived lymphocytes can be identified by differences in their electrophoretic mobility, slow cells being correlated apparently, with B-derived cells. These results can be connected with the observation that the cell coat of B-cells are rich in neutral glycoprotein containing β -fucosides and β -glucosides while the cell coat of T-cells is rich in sialoprotein and does not contain β -glucosidase-sensitive glycoprotein. Binding of ALS antibodies to lymphocytes reduces their mobility by reacting with cell coat glycoproteins. Homing abilities of lymphocytes appear to depend on cell coat glycoproteins, since the ability is lost subsequent to treatment with β -glucosidase, sialidase, and trypsin. Alteration of cell coat of lymphocytes by carbohydrases or proteases can trigger events leading to derepression of DNA synthesis in small lymphocytes. Finally, carbohydrase treatment can alter or augment the antigenicity of lymphocytes.

- 5118 LYSIS OF LEUKEMIA CELLS BY SPLEEN CELLS OF NORMAL MICE. (Eng.) Zarling, J. M. (Immunobiology Res. Center, Univ. of Wisconsin, Madison, Wis. 53706); Nowinski, R. C.; Bach, F. H. *Proc. Natl. Acad. Sci. USA* 72(7):2780-2784; 1975.

The cytotoxicity of lymphocytes of normal mouse strains that differed in incidence of spontaneous leukemia to AKR K36 leukemia cells was investigated. C57BL/6 and BALB/c mice were immunized by ip injection 2×10^7 AKR K36 cells and 1.5×10^7 Wistar-Furth (W/Fu) rat spleen cells, respectively. Cell-mediated lysis was measured *in vivo* by the ^{51}Cr release assay. Spleen cells of 2- to 3-mo-old normal mice were tested for cytotoxic activity against ^{51}Cr -labeled AKR K36 cells. By 38 hr in culture, the spleen cells of C57BL/6, C57BL/10, RF, and C57L mice mediated a significant specific ^{51}Cr release ($11 \pm 1.3\%$, $9.3 \pm 2.0\%$, $8.4 \pm 1.7\%$, and $6.6 \pm 1.6\%$, respectively) from AKR K36 cells. Incubation of ^{51}Cr -labeled AKR K36 cells with B10.BR, PL, AKR, or C58 mice spleen cells did not result in significant ^{51}Cr release. The addition of nonlabeled AKR K36 cells to the reaction mixture reduced the amount of cell-mediated cytotoxicity for ^{51}Cr -labeled AKR K36

cells to background levels. Inhibition of cell-mediated cytotoxicity was also observed when other non-labeled leukemia cells were incubated with C57BL/6 effector spleen cells and ^{51}Cr -labeled AKR K36 target cells. ERLD AND EL4 leukemia cells caused a dose-dependent inhibition of cell-mediated ^{51}Cr release from AKR K36, indicating that the antigen on AKR K36 cells (against which the C57BL/6 cells were directed) was not a normal histocompatible antigen. The addition of nonlabeled AKR or C57BL/6 thymus cells (5×10^5) resulted in only a small reduction of ^{51}Cr release from AKR K36 cells in the presence of C57BL/6 spleen cells. The addition of 1×10^5 thymus cells competitively inhibited AKR K36 spleen cell lyses of C57BL/6 mice immunized against AKR histocompatibility antigen. Pretreatment of C57BL/6 spleen cells with carbonyl iron and a magnet to remove phagocytic macrophages did not decrease the cytotoxic activity for AKR K36 cells. The results demonstrate that spleen cells from normal mice of some strains with a low incidence of spontaneous leukemia (but not high leukemic strains) lyse AKR leukemia cells *in vitro*.

- 5119 SODIUM PERIODATE STIMULATION OF HUMAN LYMPHOCYTES: A COMPARISON BETWEEN NORMAL AND CHRONIC LYMPHOCYTIC LEUKEMIA LYMPHOCYTES. (Eng.) Monahan, T. M. (Univ. Texas Medical Branch, Galveston, Tex. 77550); Fritz, R. R.; Abell, C. W. *Exp. Cell Res.* 93(2):505-508; 1975.

The conditions required for an optimal response of both normal and chronic lymphocytic leukemia (CLL) lymphocytes to NaIO_4 are reported. Normal lymphocytes respond maximally to NaIO_4 when treated at $5 \times 10^{-3}\text{M}$ (4 C for 10 min pH 7.4). Cells were maintained in McCoy's 5A media; DNA synthesis maximized later if TC199 media were used. Lymphocytes from CLL patients responded to NaIO_4 treatment (as above) with a ^3H -thymidine incorporation into DNA of 28×10^3 dpm/ 10^6 lymphocytes; maximum response to phytohemagglutinin (PHA) was about 20×10^3 dpm. The maximum response to NaIO_4 occurred at 96 hr, compared to 120 hr for PHA. The maximum response of normal lymphocytes to NaIO_4 was 15×10^3 dpm at 48 hr; the response to PHA was 26×10^3 dpm at 72 hr. NaIO_4 is a unique agent for probing the surface architecture of lymphocytes.

- 5120 LYMPHOCYTES AND LEUKEMIA VIRUSES: TROPISM AND TRANSTROPISM OF MURINE LEUKEMIA VIRUS. (Eng.) Datta, S. K. (New England Medical Center Hosp., 171 Harrison Ave., Boston, Mass. 02111); Melief, C. J. M.; Schwartz, R. S. *J. Natl. Cancer Inst.* 55(2):425-432; 1975.

Principles of murine leukemia virus (MuLV) N-tropism (replication in NIH Swiss fibroblasts) and B-tropism (replication in BALB/c fibroblasts) were tested in corresponding lymphocyte cultures from the two mouse strains. Such studies appeared relevant to the natural history of MuLV because the major oncogenic effect of this virus is expressed *in vivo* in lymphocytes. N-tropic virus was obtained in the form of clarified supernatants from NIH Swiss mouse embryo fibroblasts (MEF) cultures that had been cocultivated

with AKR lymphocytes; B-tropic virus was obtained as supernatant from BALB/c MEF cultures cocultivated with B10.A lymphocytes. Tests for infection of virus-negative lymphocytes and MEF were carried out by adding virus-containing supernatants to spleen cell suspensions or fresh MEF monolayers, culturing for six days, treating the cultures with mitomycin, and finally titrating for MuLV. Stimulation of lymphocytes was carried out under conditions of mixed lymphocyte culture (MLC), using a mixture of mitomycin-treated stimulating cells and allogeneic responding cells. Evidence for stimulation was based on measurement of uptake of ^3H -thymidine. Lymphocytes free of infectious MuLV could be infected across the tropism barrier by virus-containing supernatants or by *in vitro* contact with MuLV-producing lymphocytes. Stimulation of the lymphocytes was not required for this cross-infection and replication of MuLV. When cross-infected lymphocytes were stimulated *in vitro* by allogeneic cells, however, they facilitated MuLV infection of ordinarily nonpermissive fibroblasts. This phenomenon, called transtropism, required antigenically stimulated lymphocytes and was specifically associated with infection of the lymphocyte by MuLV across the tropism barrier. Thus, in contrast with the resting lymphocyte, the transformed lymphocyte acquired the ability to disseminate infectious MuLV to nonpermissive cells. This phenomenon may be important in the pathogenesis of leukemias and lymphomas, especially those that arise against a background of persistent antigenic stimulation.

- 5121 LYMPHOCYTE REACTIVITY IN PATIENTS WITH CARCINOMA OF THE BREAST AND LARGE BOWEL. (Eng.) Miller, J. J. (Univ. Bristol, The Medical Sch., Univ. Walk, Bristol BS8 1TD, England); Gaffney, P. R.; Rees, J. A.; Symes, M. O. *Br. J. Cancer* 32(1):16-20; 1975.

The reactivity of lymphocytes from patients with either carcinoma of the breast or large bowel was studied using the human to mouse normal lymphocyte transfer (NLT) reaction. Lymphocytes of 38 patients with breast carcinoma, 18 patients with large bowel carcinoma, 15 patients with benign breast neoplasms, and 17 patients with nonneoplastic conditions were studied. Five to ten million cells in 0.1 ml were injected *id* into an outbred Ash Porton mouse on day zero. The diameter of the NLT was measured on day two. In the case of breast cancer, there was a direct correlation between the clinical stage and a reduced NLT reaction. Only patients with regional lymph node or generalized metastases showed significantly reduced lymphocyte reactivity. However, in the case of large bowel cancer there was a generalized reduction in NLT reactivity which was independent of the clinical stage. Incubation of lymphocytes from individuals without neoplastic disease in serum or plasma from breast cancer patients, showing reduced NLT reactivity, resulted in a reduced NLT reaction. This appears to be indicative of the presence of circulating "blocking factor" in such patients.

- 5122 QUANTITATIVE AGGLUTINATION OF SPECIFIC POPULATIONS OF SEA URCHIN EMBRYO CELLS WITH CONCAVALIN A. (Eng.) Roberson, M. (Dep.

Biol., California State Univ., Northridge); Oppenheimer, S. B. *Exp. Cell Res.* 91(2):263-268; 1975.

In view of the demonstration that specific changes in carbohydrate-containing cell surface lectin receptor sites occur with differentiation and maturation of sea urchin embryo cells, a quantitative electronic particle counter assay of agglutination was carried out. Evidence was obtained indicating that concanavalin A (Con A)-mediated agglutination of dissociated (32/64 cell stage) sea urchin embryos differs dramatically with respect to specific cell populations. The migratory cell type, the micromere, is significantly more agglutinable with 1 mg/ml Con A than the other cell types and colchicine treatment (0.001 M) markedly increases sea urchin embryo cell agglutinability. The results indicate that like many malignant cells which display expensive migratory behavior, specific migratory populations of embryonic cells are agglutinable with Con A. The results are discussed with respect to the possible nature of lectin receptor sites on specific populations of embryonic cells and the possible role of colchicine-sensitive structures in controlling the display patterns of these sites. Structures sensitive to the drug may anchor Con A receptor sites in a pattern which inhibits the mobility of these sites and cell agglutination. Disruption of these structures with colchicine could free lectin binding sites, allowing increased mobility and cell agglutination.

5123 CARCINOGENESIS IN TISSUE CULTURE 88: ON THE BACK-TRANSPLANTATION TESTS OF CULTURED MAMMALIAN CELLS [abstract]. (Jpn.) Sakakibara, K. (Inst. Medical Sci., Univ. Tokyo, Tokyo, Japan); Takaoka, T.; Katsuta, H. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 25.

5124 GRAFT VERSUS HOST REACTION AND MALIGNANT LYMPHOMA DEVELOPMENT IN MICE [abstract]. (Eng.) Nakakuki, K. (Mie Univ. Sch. Medicine, Tsu, Japan). *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 21.

5125 INDUCTION OF TRANSPLANTATION IMMUNITY TO TUMOR BY FLUORESCENT LABELED VIABLE TUMOR CELLS [abstract]. (Jpn.) Hashimoto, Y. (Tokyo Biochemical Res. Inst., Tokyo, Japan); Yamanoha, B. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 55.

5126 THE ROLE OF A TUMOR CELL AGGLUTINATING FACTOR INDUCED IN TUMOR-BEARING ANIMALS IN THE INDUCTION OF TRANSPLANTATION IMMUNOGENICITY [abstract]. (Eng.) Egawa, K. (Inst. Medical Sci., Univ. Tokyo, Tokyo, Japan); Tanino, T. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 54.

5127 IMMUNOLOGICAL STUDIES ON AUTOCHTHONOUS RAT TUMORS INDUCED BY MOLONEY SARCOMA VIRUS (MSV-M). (III). MECHANISMS OF REGRESSION AND REGROWTH [abstract]. (Eng.) Yoshida, T. O. (Hamamatsu Univ. Sch. Medicine, Hamamatsu, Honshu, Japan); Tanaka, K. K.; Kojima, K.; Hanaichi, T. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 58.

5128 SPECIFIC LYMPHOCYTE BLASTOGENESIS AND ANTI TUMOR RESISTANCE IN HUMAN CANCER PATIENTS [abstract]. (Jpn.) Yamaoka, H. (The First Dept. of Pathology, Sapporo Med. Coll., Sapporo, Japan); Kanaya, T.; Ishii, Y.; Koshiba, H.; Ishibashi, F.; Kikuchi, K. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 53.

5129 CROSS-IMMUNITY AMONG SYNGENEIC TUMORS IN MICE IMMUNIZED WITH GAMMA-IRRADIATED TUMOR CELLS [abstract]. (Jpn.) Ito, I. (Hirosaki Univ. Sch. Medicine, Hirosaki, Japan); Nishimura, S.; Kudo, H.; Sobajima, Y.; Usubuchi, I. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 56.

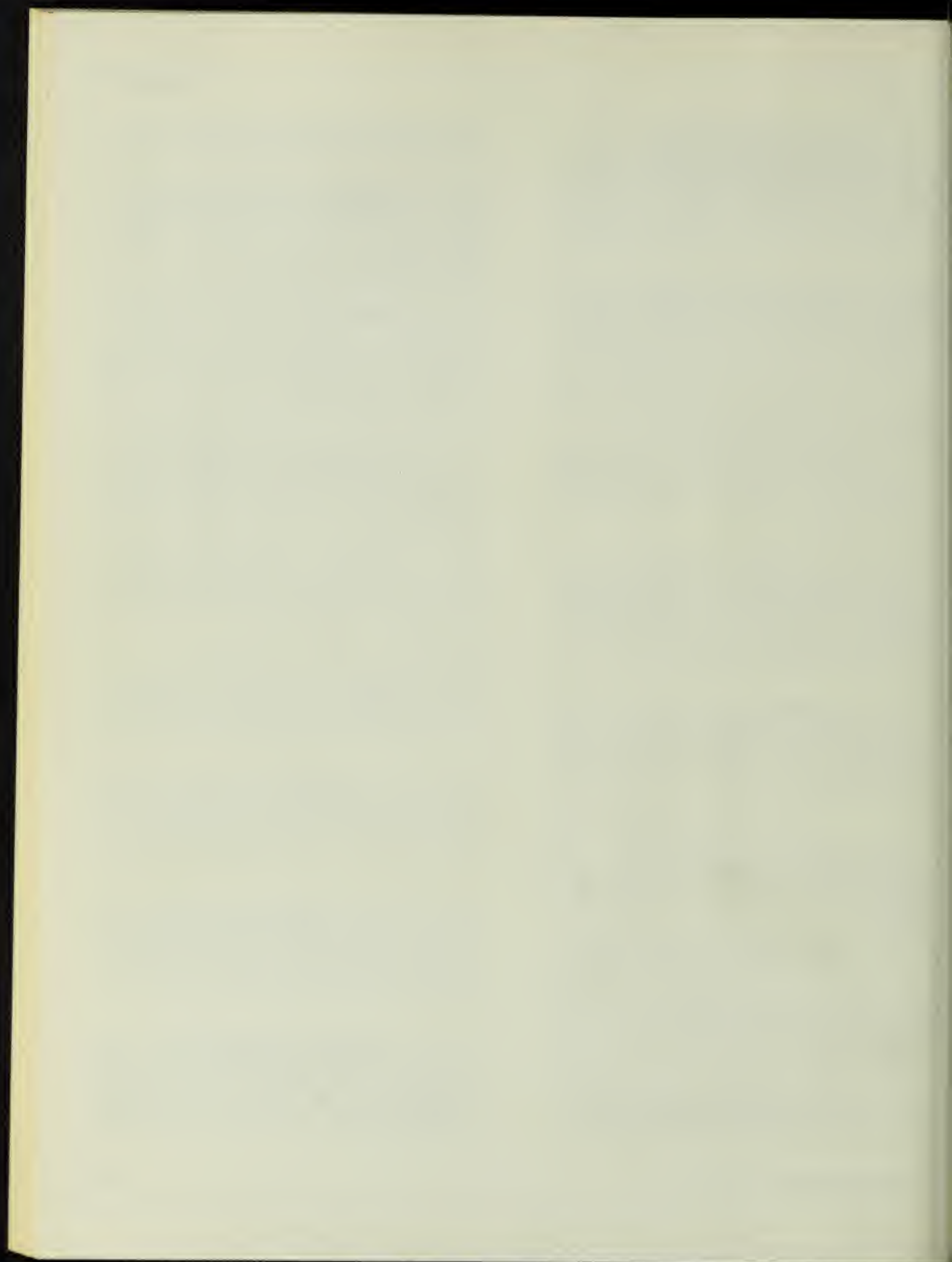
5130 LOCAL ADOPTIVE TRANSFER OF THE ANTITUMOR CELLULAR IMMUNE RESPONSE IN SYNGENEIC AND ALLOGENEIC MICE STUDIED WITH A RAPID RADIOISOTOPIC FOOTPAD ASSAY [abstract]. (Eng.) Takeichi, N. (Natl. Cancer Inst., Natl. Inst. Health, Bethesda, Md.); Boone, C. W. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 57.

5131 EXPERIMENTAL TRIAL TO AUGMENT THE DEVELOPMENT OF CELL-MEDIATED IMMUNITY BY T-T CELL INTERACTION [abstract]. (Jpn.) Toshima, K. (Inst. Cancer Res., Osaka Univ. Medical Sch., Osaka, Japan); Hamaoka, T.; Fujiwara, H.; Nishino, Y.; Kitagawa, M. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 55.

5132 RELATIONSHIP BETWEEN THE MORPHOLOGICAL CHANGES IN THE LYMPH NODES OF GASTRIC CANCER PATIENTS AND THE CELLULAR IMMUNITY OF LYMPH NODES [abstract]. (Jpn.) Tanaka, T. (Kyoto Pref. Univ. Medicine, Kyoto, Japan); Kodama, M.; Fujita, M.; Inaba, S.; Koshiba, H.; Ishibashi, F.; Kikuchi, K. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 52.

5133 STUDIES OF REGULATORY MECHANISMS OF CELLULAR IMMUNITY IN NEOPLASTIC DISEASES. 4. COMPARISON OF IMMUNOSUPPRESSIVE FACTORS IN SERUM FROM PATIENTS WITH MALIGNANT AND BENIGN DISEASES [abstract]. (Jpn.) Nagai, T. (Cancer Res. Inst., Sapporo Medical Coll., Sapporo, Japan); Gocho, Y.; Kondo, A.; Yoshida, N.; Koyama, R.; Urushizaki, I. *Gann, Proc. Jpn. Cancer Assoc.*, 34th Annual Meeting, October 1975. p. 50.

- 5134 DIMINISHED IMMUNOLOGICAL CAPACITY IN TUMOR-BEARING ANIMALS. (IV). PURIFICATION AND CHARACTERIZATION OF AN IMMUNOSUPPRESSIVE FACTOR FROM EHRlich CARCINOMA ASCITES [abstract]. (Jpn.) Motoki, H. (Tohoku Univ. Sch. Medicine, Sendai, Japan); Kitame, F.; Ishida, N. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 50.
- 5135 STUDIES OF REGULATORY MECHANISMS OF CELLULAR IMMUNITY IN NEOPLASTIC DISEASES. 3. ON THE DIFFERENCE OF INHIBITORY EFFECT AGAINST LYMPHOCYTE BLASTOGENESIS OF SERUM FACTORS FROM PATIENTS WITH CARCINOMA [abstract]. (Jpn.) Gocho, Y. (Cancer Res. Inst., Sapporo Medical Coll., Sapporo, Japan); Nagai, T.; Yoshida, N.; Kondo, A.; Tamura, M.; Urushizaki, I. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 50.
- 5136 REACTIVITY OF GASTRIC CANCER AND NORMAL GASTRIC MUCOSA EXTRACTS WITH THEIR IMMUNE ANTISERA [abstract]. (Jpn.) Aizawa, F. (Sch. Medicine, Gunma Univ., Maebashi, Japan); Furukawa, K. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 55.
- 5137 PROGNOSTIC VALUE OF DELAYED CUTANEOUS HYPERSENSITIVITY, PERIPHERAL LYMPHOCYTE COUNTS AND IMMUNOGLOBULIN IN PATIENTS WITH CANCER [abstract]. (Jpn.) Sakurai, T. (Nat'l. Sapporo Hosp. Hokkaido Cancer Center, Sapporo, Hokkaido, Japan). *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 51.
- 5138 A NEW COMMON MARKER FOR PREMALIGNANT AND MALIGNANT HEPATOCYTES INDUCED IN THE RAT BY CHEMICAL CARCINOGENS [abstract]. (Eng.) Okita, K. (Yamaguchi Univ., Sch. Medicine, Ube, Japan). *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 18.
- 5139 HL-A ANTIGENS OF LARGE INTESTINAL CANCER AND FAMILIAL POLYPOSIS [abstract]. (Jpn.) Yagita, A. (Keio Univ. Sch. Medicine, Tokyo, Japan); Morioka, A.; Baba, S.; Sekiguchi, S.; Abe, O. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 49.
- 5140 ANTIBODY PRODUCTION IN TUMOR-BEARING ANIMALS. (XI.) MECHANISM OF SELECTIVE T-CELL SUPPRESSION IN TUMOR-BEARING MICE [abstract]. (Jpn.) Hara, S. (Inst. for Cancer Res., Osaka Univ. Medical Sch., Osaka, Japan); Hamaoka, T.; Kitagawa, M. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 50.
- 5141 LYMPHOCYTE RESPONSE TO PHA AND PWM IN CANCER PATIENTS [abstract]. (Jpn.) Toge, T. (Res. Inst. Nuclear Medicine Biology, Univ. Hiroshima, Hiroshima, Japan); Terao, H.; Hattori, T. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 52.
- 5142 IMMUNOLOGICAL CROSS REACTION BETWEEN SERA FROM PATIENTS WITH BREAST CANCER AND MOUSE MAMMARY TUMOR CELL LINE [abstract]. (Jpn.) Imai, M. (Aichi Cancer Center Res. Inst., Nagoya, Japan); Hoshino, M. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 55.
- 5143 IMMUNOHISTOLOGY OF THE ANTIGENIC PATTERN OF A CONTINUOUS CELL LINE FROM A HUMAN COLON TUMOR. (Eng.) von Kleist, S. (Institut de Recherches Scientifiques sur le Cancer, B. P. No. 8, 7, Rue Guy-Mocquet, 95800 Villejuif, France); Chany, E.; Burtin, P.; King, M.; Fogh, J. *J. Natl. Cancer Inst.* 55(3):555-560; 1975.
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- 5148 ROLE OF A NON-COMMITTED ACCESSORY CELL IN THE *IN VIVO* SUPPRESSION OF A SYNGENEIC TUMOUR BY IMMUNE LYMPHOCYTES. (Eng.) Simes, R. J. (Royal North Shore Hosp., St. Leonards, New South Wales 2065, Australia); Kearney, R.; Nelson*, D. S. *Immunology* 29(2):343-351; 1975.
- 5149 IMMUNOLOGIC ASPECTS OF 1,2-DIMETHYLHYDRAZINE-INDUCED COLON TUMORS IN RATS. (Eng.) Garmaise, A. B.-K. (Dept. Nutrition and Food Sci., Massachusetts Inst. Technology, Cambridge, Mass. 02139); Rogers*, A. E.; Saravis, C. A.; Zamcheck, N.; Newberne, P. M. *J. Natl. Cancer Inst.* 54(5):1231-1235; 1975.



- 5150 IMMUNE SURVEILLANCE OF NATURALLY OCCURRING FELINE LEUKEMIA [abstract]. (Eng.) Essex, M. (Harvard Univ. Sch. Public Health, Boston, Mass.); Cotter, S.; Hardy, W. D., Jr. *Proc. Am. Assoc. Cancer Res.* 16:126; 1975.
- 5151 IMMUNOPROPHYLAXIS AND CYTOTOXIC EFFECTOR CELLS AGAINST EL 4 LEUKEMIA INDUCED IN SYNGENEIC C57BL/6J MICE BY USE OF IRRADIATED EL 4 CELLS. (Eng.) Johnson, T. S. (Univ. of Miami Sch. Medicine, Miami, Fla. 33136); Hudson, J. L.; Feldman, M. E.; Irvin, G. L., III. *J. Natl. Cancer Inst.* 55(3):561-567; 1975.
- 5152 IMMUNOSUPPRESSIVE EFFECT OF HUMAN MALIGNANT TISSUE EXTRACTS COMBINED WITH POLYCYTHEMIC FRIEND VIRUS SFFV-LLV COMPLEX (PF) [abstract]. (Eng.) Fjelde, A. (Roswell Park Mem. Inst., Buffalo, N.Y.); Evege, E.; Oleszek, D. *Proc. Am. Assoc. Cancer Res.* 16:78; 1975.
- 5153 ALTERED IMMUNOLOGIC SPECIFICITY OF CELLS INFECTED WITH HERPES SIMPLEX VIRUS: RECOGNITION BY HUMAN ANTISERUM. (Eng.) Schwartz, J. (Mt. Sinai Sch. Med. City Univ. New York, N.Y.); Elizan, T. S. *Z. Immunitaetsforsch.* 148(4):291-298; 1975.
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- 5162 DEMONSTRATION OF UNIQUE AND NOT COMMON TUMOR SPECIFIC TRANSPLANTATION ANTIGENS IN POLYOMA VIRUS-INDUCED TUMORS [abstract]. (Eng.) Mattison, R. A. (Dept. Pediatr., Univ. Washington, Seattle); Bernstein, I. D.; Wright, P. W. *Proc. Am. Assoc. Cancer Res.* 16:85; 1975.
- 5163 INVESTIGATION OF FETAL ANTIGEN IN CHICKENS WITH AMV-INDUCED LEUKEMIA. (Eng.) Sanders, B. G. (Univ. Texas, Zoology Dept., Austin, Tex.); Teplitz, R. L.; Brodestsky, A. M.; Fung, H.; Wiley, K. L. *Cell Cycle in Malign. Immun., Proc. Annu. Hanford Biol. Symp., 13th.* Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 348-358.
- 5164 TRANSFORMATION-ASSOCIATED SURFACE ANTIGEN COMMON TO CHICK EMBRYO CELLS MORPHOLOGICALLY ALTERED BY DIFFERENT AVIAN ONCORNAVIRUSES [abstract]. (Eng.) Morris, R. E. (Emory Univ., Atlanta, Ga.). *Diss. Abstr. Int. B* 35(11):5503; 1975.
- 5165 AN IMMUNOELECTRON MICROSCOPIC STUDY OF CELL SURFACE ANTIGENS INDUCED BY AVIAN TUMOR VIRUSES. (Eng.) Phillips, E. R. (Univ. Wisconsin-Madison). *Diss. Abstr. Int. B* 35(11):5253; 1975.
- 5166 LYMPHOCYTE FUNCTIONS IN THE RAT SPLEEN AT VARIOUS TIMES AFTER URETHAN ADMINISTRATION. (Eng.) Di Marco, A. T. (Istituto di Cancrologia dell'Universita degli Studi, Bologna, Italy); Macario, A.; Xerri, L.; Prodi, G. *Tumori* 61(4):319-326; 1975.
- 5167 EVIDENCE OF AN INTRINSIC DEFECT OF LYMPHOCYTE REACTIVITY IN AKR MICE. (Ita.) Collavo, D. (Istituto di Anatomia Patologica dell'Universita, Padova, Italy); Biasi, G.; Colombatti, A.; Varotto, M.; Fabbris, R. *Tumori* 61(4):339-349; 1975.

- 5168 QUANTITATION OF POTENTIAL T-LYMPHOCYTE FUNCTION IN RATS. (Eng.) Miller, T. E. (Univ. of Auckland Sch. Medicine, Auckland 3, New Zealand); Creaghe, E. *Infect. Immun.* 12(4):722-727; 1975.
- 5169 ADJUVANT AND MITOGENIC ACTIVITY OF DETOXIFIED LIPOPOLYSACCHARIDES. (Fre.) Chedid, L. (Service d'Immunotherapie Experimentale, Institut Pasteur, 25, rue du Docteur-Roux, 75015 Paris, France); Audibert, F.; Bona, C. *C. R. Acad. Sci. [D] (Paris)* Vol. 280(9):1197-1200; 1975.
- 5170 A MITOGENIC FACTOR OF HUMAN LYMPHOCYTES INDUCED BY PHYTOHEMAGGLUTININ. (Rus.) Voitenok, N. N. (Dept. Hematol., Belorussian Inst. Hematol. Blood Trans., Minsk, U.S.S.R.). *Probl. Hematol. Pereliv. Krovi* 20(3):48-51; 1975.
- 5171 LYMPHOCYTE BLASTOGENESIS INDUCED BY POTASSIUM CHLORIDE EXTRACTS OF ALLOGENEIC BREAST CARCINOMA AND LYMPHOID CELLS. (Eng.) Dean, J. H. (Litton Bionetics, Inc., 5516 Nicholson Lane, Kensington, Md. 20795); Silva, J. S.; McCoy, J. L.; Leonard, C. M.; Middleton, M.; Cannon, G. B.; Herberman, R. B. *J. Natl. Cancer Inst.* 54(6):1295-1298; 1975.
- 5172 TRANSFORMATION RESPONSE AND T-CELL CONTENT OF THORACIC AND BLOOD LYMPHOCYTES. (Eng.) Benninghoff, D. L. (Huntington Hosp., Huntington, N.Y.); Girardet, R. E.; Porteous, D. D. *Cell Cycle in Malign. Immun., Proc. Annu. Hanford Biol. Symp.*, 13th. Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 574-582.
- 5173 STUDY OF THE CORRELATIONS BETWEEN AGGLUTINABILITY BY CONCAVALIN A AND POLYOMA VIRUS-INDUCED NUCLEIC ACID SYNTHESIS. (Fre.) Barra, Y. (Unite 119 de l'INSERM, 27, boulevard Lei Roure, 13009 Marseille, France); Meyer, G. *C. R. Acad. Sci. [D] (Paris)* Vol. 280(9):1205-1208; 1975.
- 5174 CONCAVALIN A AGGLUTINATION OF CELLS FROM PRIMARY HEPATOCELLULAR CARCINOMAS AND HEPATIC NODULES INDUCED BY N-2-FLUORENYLACETAMIDE. (Eng.) Becker, F. F. (New York Univ. Sch. Medicine, New York, N.Y. 10016); Shurgin, A. *Cancer Res.* 35(10):2879-2883; 1975.
- 5175 QUANTITATION OF VIRUS-INDUCED (MLr) AND NORMAL (Thy.1.2) CELL SURFACE ANTIGENS IN ISOLATED PLASMA MEMBRANES AND THE EXTRACELLULAR ASCITES FLUID OF MOUSE LEUKEMIA CELLS. (Eng.) Van Blitterswijk, W. J. (The Netherlands Cancer Inst., Antoni van Leeuwenhoek-Lab., Sarphatistraat 108, Amsterdam, The Netherlands); Emmelot, P.; Hilgers, J.; Kamlag, D.; Nusse, R.; Feltkamp, C. A. *Cancer Res.* 35(10):2743-2751; 1975.
- 5176 IMMUNOLOGIC, VIROLOGIC, AND GENETIC ASPECTS OF MAMMARY TUMOR VIRUS-INDUCED CELL-SURFACE ANTIGENS: PRESENCE OF THESE ANTIGENS AND THE THY 1.2 ANTIGEN ON MURINE MAMMARY GLAND AND TUMOR CELLS. (Eng.) Hilgers, J. (Netherlands Cancer Inst., 108 Sarphatistraat, Amsterdam-1004, Netherlands); Haverman, J.; Nusse, R.; van Blitterswijk, W. J.; Cleton, F. J.; Hageman, P. C.; van Nie, R.; Calafat, J. *J. Natl. Cancer Inst.* 54(6):1323-1333; 1975.
- 5177 CULTURED HUMAN LYMPHOID CELLS: TOOLS FOR THE BIOLOGICAL AND MOLECULAR CHARACTERIZATION OF ANTIGENS AND THEIR RECOGNITION SYSTEMS. (Eng.) Reisfeld, R. A. (Scripps Clinic and Res. Foundation, 476 Prospect St., La Jolla, Calif. 92037); Pellegrino, M. A.; Dierich, M. P.; Ferrone, S. *In Vitro* 11(4):173-185; 1975.
- 5178 IMMUNOCYTOADHERENCE OF HUMAN LYMPHOCYTES IN LYMPHO-PROLIFERATIVE DISORDERS [abstract]. (Eng.) Beaumariage, M. L. (Laboratoire d'Anatomie Pathologique, Hopital de Baviere, B-4002 Liege, Belgium); Focan, C. *IRCS Med. Sci.* 3(9):476; 1975.
- 5179 LOCAL LYMPHO-PLASMACELLULAR REACTION TO PRECANCEROUS LESIONS AND TUMOURS OF VARIOUS ORGANS IN MAN. (Eng.) Maltoni, C. (Istituto di Oncologia "F. Addarii", Bologna, Italy). *Parminerva Med.* 17(5/6):167-169; 1975.
- 5180 PREOPERATIVE AND POSTOPERATIVE LYMPHOCYTE RESPONSE TO P.H.A. IN CANCER PATIENTS. (Eng.) Sega, E. (Laboratorio di Immunologia, Istituto Regina Elena di Roma, Italy); Vasile, C.; Di Paola, M.; Colizza, S.; Benvenuti, C.; Catini, F.; Midiri, G. *Surg. Italv* 4(3):188-194; 1974.
- See also:
- * (Rev): 4807, 4808, 4809, 4836, 4837, 4838, 4839, 4840
 - * (Viral): 5010, 5012, 5026, 5059, 5061, 5062, 5063
 - * (Path): 5190, 5192, 5205, 5242, 5253, 5259
 - * (Epid-Biom): 5296

PATHOGENESIS

- 5181 SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY--CHRONIC ORAL ULCERATIVE DISEASE AS A POSSIBLE ETIOLOGIC FACTOR. (Eng.) Faraci, R. P. (Nat'l. Cancer Inst., Bethesda, Md.); Schour, L.; Graykowski, E. A. *J. Surg. Oncol.* 7(1):21-26; 1975.

The association of carcinoma of the oral cavity with chronic oral ulcerative disease was documented in two female patients. The first patient (79 yr old) had an almost 40-yr history of intermittent oral pain and tenderness associated with the formation of whitish plaques which would break down and ulcerate. Biopsy of the ulcerated area showed lichen planus, for which the patient was treated symptomatically for 14 yr. After this time, another biopsy showed well-differentiated squamous carcinoma where lichen planus had been present. The patient received radiotherapy and 4 mo following treatment remained tumor-free. This patient had discontinued intermittent smoking 14 yr prior to the cancer development. The second patient (62-yr-old) had developed oral mucosal blisters which were diagnosed as pemphigus vulgaris. Examination revealed vesicobullous lesions with associated erosions involving the entire buccal mucosa and gingiva, as well as the dorsum and undersurface of the tongue. Prednisone treatment resulted in significant regression in the lesions. Over the next 3 yr, however, the lesions persisted and new lesions involving the tongue, right lateral hard palate, and right tonsil developed. Biopsies of these areas revealed squamous cell carcinoma which was treated with radiotherapy. After several regressions followed by recurrences, the patient underwent total glossectomy with bilateral suprathyroid neck dissection, but died with massive local recurrence in the oropharynx. This patient had no history of cigarette smoking, alcohol intake, or ingestion of irritating substances. The absence of known etiologic agents for oral cancer in these two patients suggests that chronic irritation associated with longstanding epithelial disorders led to the development of the oral cancers.

- 5182 THREE YEAR FOLLOW UP STUDY OF TOLUIDINE BLUE POSITIVE AND NEGATIVE HARD PALATE ULCERS IN REVERSE SMOKING FEMALES. (Eng.) Reddy, C. R. R. M. (Andhra Medical Coll., Visakhapatnam-2, S. India); Mouli, K. C.; Kameswari, V. R. *Indian J. Cancer* 12(2):113-117; 1975.

The use of cheap toluidine blue staining of the oral cavity in following up dysplastic lesions was evaluated. In three villages, 1,673 people were surveyed and examined. Ulcers of the hard palate and large umbilicated papules of stomatitis nicotina were stained with toluidine blue. In the 208 reverse smoking females with stomatitis nicotina, 30 had hard palate ulcers. However, no palatal ulcers were found in 60 reverse smoking males examined. Of the 30 hard palate ulcers, 22 were negative for toluidine blue and eight were positive. Over three years, three of the positive ulcers grew larger and macroscopically became cancer. Two cases became negative for toluidine blue, three continued positive, and two originally negative ulcers became toluidine blue positive. All carcinomas tested were found to stain blue, as did palatal nevi and areas of dysplasia. Biopsied

stomatitis nicotina lesions showed 13% false negatives and 11% false positives. It is concluded that toluidine blue staining of precancerous and cancerous lesions of the oral cavity could be used in large scale mass surveys; it is very cheap, quick, and obviates a biopsy.

- 5183 ELECTRON MICROSCOPICAL STUDIES ON THE CONNECTIVE-TISSUE STROMA IN BASAL CELL EPITHELIOMA. (Pol.) Kozakiewicz, J. (80-211 Gdansk, Klinika Dermatologiczna AM, ul. Debinki 7., Poland); Wrzolkowa, T. *Przegl. Dermatol.* 62(3):335-339; 1975.

Comparison of biopsy material obtained from six cases of solid basocellular epithelioma with that from six cases of adenoid basocellular epithelioma revealed differences in the connective tissue stroma of the 2 forms. Histologically, the former was characterized by extensive, uniform neoplastic foci surrounded by dense connective tissue; the latter was characterized by dispersed small foci of epithelioma in a loose, swollen connective tissue base. Electron microscopy revealed that, in the solid form, the basement membrane was either broadened, fragmented or, rarely, missing. The connective tissue stroma showed a mixture of different types of fibrous elements exhibiting signs of stimulation and various degrees of maturation. In the dispersed form of epithelioma (adenoid) the basement membrane was either pushed away from the cells of the epithelioma, fragmented or, frequently, absent. This was accompanied by a penetration of fibrous elements into the neoplastic focus. The connective tissue stroma showed extensive accumulations of granular substrate indicating the presence of mucopolysaccharides with dispersed collagen fibers.

- 5184 POIKILODERMA ATROPHICANS VASCULARE AS A POINTER TO RETICULOSIS OF THE SKIN. (Eng.) Chapman, R. S. (Stobhill General Hosp., Glasgow G21 3UW, Scotland); Paul, C. J. *Postgrad. Med. J.* 51(597):463-467; 1975.

A case of poikiloderma atrophicans vasculare preceeding mycosis fungoides and terminal reticulum cell sarcoma by 40 yr is described. A 63-yr-old man with a 40-yr history of progressively extending areas of redness and scaling on his trunk presented with skin ulcers, striking pigmentation, and features of poikiloderma atrophicans vasculare. Histological examination of skin biopsies showed atrophy of the epidermis with liquefaction degeneration of the basal layer. There was marked subepidermal edema, marked telangiectasia, many pigment-laden macrophages, and suggestions of mycosis fungoides or lymphoma. Prednisone initially effected rapid healing of all ulcer sites, then became increasingly ineffective. Subsequent hip pain and orthopedic examination indicated disease of the right sacro-iliac joint. Death occurred suddenly due to pulmonary embolism. Autopsy and histological examination revealed replacement and infiltration of the psoas muscle by histiocyte-like cells, and nodules in the spleen, thyroid gland, and abdominal lymph nodes. The final

pathological diagnosis was pleomorphic reticulum cell sarcoma or malignant diffuse nodular pleomorphic histiocytic lymphoma. It is concluded that the patient had progressive involvement of head, arms, and trunk by poikiloderma atrophicum vasculare over 40 yr, progressive increase in malignancy, and systemic spread as reticulum cell sarcoma.

- 5185 BASAL CELL NAEVUS SYNDROME: REPORT OF A CASE AND REVIEW OF THE LITERATURE. (Eng.) Mangala, P. B. (Dept. Pathology, Medical Coll., Aurangabad, India); Sengupta, S. R.; Krishnan, E. C. *Indian J. Cancer* 12(2):214-218; 1975.

A case of basal cell nevus syndrome, with the unusual association of a malignant melanoma of the nasal mucosa, is presented. The 22-yr-old man had a mass in left nostril, frequent episodes of epistaxis, symmetrical, 3-4 mm raised lesions all over the body, and leukoplakic patches on both lips. There were no abnormal radiological, liver function, hematological, or endocrine abnormalities, nor any family history of similar lesions. Histological examination of the nasal tumor at biopsy and after excision revealed a malignant melanoma. Biopsy of several cutaneous lesions showed basal cell epithelioma. A brief literature review of the syndrome notes striking analogies between cutaneous and jaw lesions, a pathogenesis suggesting an in-born metabolic defect, and inheritance as an autosomal dominant polymorphic trait with good penetrance and variable expressivity.

- 5186 ARGYROPHIL CELL MICRONEPLASIA IN THE MASTOMYS' STOMACH--AN OBSERVATION ON EARLY CARCINOID FORMATION. (Eng.) Soga, J. (Univ. Niigata Sch. Medicine, Niigata City, Japan 951); Kohro, T.; Tazawa, K.; Kanahara, H.; Sano, M.; Sakashita, T.; Tajima, K.; Morooka, H.; Karaki, Y. *J. Natl. Cancer Inst.* 55(4):1001-1006; 1975.

To analyze the early stages of argyrophil cell carcinoid growth, complete serial sections were cut from the glandular portion of the stomachs of 22 *Mastomys* (an African rodent) and subjected to Sevier-Munger's reaction. The 154 grossly invisible foci of argyrophil cell microproliferation thus detected were classified into three stages of microproliferations (I, II, and III), and the last stage was definitely a microcarcinoid. There was a gradual transition in cell proliferation among these three stages; the first stage (microproliferation I), in which the cells were morphologically indistinguishable from those of hyperplastic proliferation by general morphologic criteria, was where the initial change of argyrophil cell carcinoid formation was detectable by a light microscope. Whereas multiple occurrences of microcarcinoids accounted for the multiplicity of well-developed tumors in the stomachs of *Mastomys*, a well-developed carcinoid in this species was formed by the confluence of several microcarcinoids.

- 5187 THE RELATIONSHIP OF GASTROINTESTINAL ENDOCRINE CELLS TO GASTRIC EPITHELIAL CHANGES WITH SPECIAL REFERENCE TO GASTRIC CANCER.

(Eng.) Tahara, E. (Hiroshima Univ. Sch. Med., Japan); Haizuka, S.; Kodama, T.; Yamada, A. *Acta Pathol. Jpn.* 25(2):161-177; 1975.

The relationship of gastric endocrine cells to gastric cancer was studied morphologically using tissue samples from 159 cases of human gastric cancer, five cases of human primary gastric carcinoid, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)-induced rat (Wistar) gastric cancer, and x-ray-induced mouse (ICR/JCR) gastric adenocarcinoma. The tissues were examined by light, fluorescence, and electron microscopy. Among the human gastric cancer tissues, there was a tendency for silver-positive cells, especially argyrophil cells within cancer cells, to appear more frequently in undifferentiated adenocarcinomas than in differentiated adenocarcinomas. Reactive proliferation of argentaffin cells was frequently observed in the metaplastic and nonmetaplastic epithelium surrounding the cancer as well as in the atypical epithelium of benign and malignant borderline lesions. Among the human carcinoid cases, there was one case of mixed argyrophil cell type, one case of B type argyrophil cell type, and three cases of nonreactive cell type (one type A and two mixed type). Electron microscopy revealed special secretory granules in all nonreactive cell types. In one case, a definite transition between an adenocarcinoma and carcinoid was demonstrated. None of the carcinoid cases presented clinical symptoms of endocrine abnormality. The MNNG-induced cancers first presented as an adenomatous hyperplasia, which often exhibited acid mucus. Adenocarcinoma subsequently developed, silver positive cells being scattered within the cancer tissue. Some cancer cells contained both mucus and endocrine granules. X-irradiation was also followed by the development of atypical glandular hyperplasia containing cells with acid mucus. Adenocarcinoma then developed, the frequency of silver-positive cells being reduced in these cells compared to the MNNG-induced adenocarcinoma cells. Argentaffin cells were seen in some cancer cells undergoing differentiation into intestinal metaplasia, and cancer cells containing endocrine secretory granules were observed. The results indicate that most of the endocrine cells observed in the cancer tissues were derived from the differentiation of cancer cells. Argentaffin cells appear to be related to the development of intestinal metaplasia in the gastric mucosa.

- 5188 CYTOLOGIC STUDIES ON SO-CALLED ATYPICAL EPITHELIUM OF THE PROTUBERANT LESIONS IN THE STOMACH. (Eng.) Takeda, T. (Miyagi Prefectural Center for Adult Diseases, Natori City, Miyagi Prefecture, Japan); Takaso, K.; Isono, S.; Sato, M.; Sato, E.; Ishioka, K. *Acta Cytol. (Baltimore)* 19(4):345-350; 1975.

The cytology of "atypical epithelial growth" (ATP) in the gastric mucosa and the histologic evaluation of an atypical growth pattern were studied. Cytologic studies based on the observation of 32 atypical epithelial growths from 31 patients revealed the following characteristics. The nuclei

were usually elongated. Of the 13 mild lesions, the ratio of the minor axis: major axis length was under 0.6; 4 of the 9 severe lesions had a ratio above 0.6. In all six cases of adenocarcinoma studied for comparison, this ratio was over 0.6. The cells were heaped together. A cellular aggregation was clearly composed of smaller groups of cells in which the polarity of nuclear arrangement was well preserved. Some cells at the periphery of a cellular aggregation were arranged radially toward the outside. The cells were usually cohesive, but in severe grade of atypism, they sometimes showed a scattering tendency. Two cases were irradiated with 3,600 and 4,200 rads. The cells of atypical epithelium seemed to be very insensitive to radiation, compared with carcinoma cells of the stomach. The pattern of ATP cells was more disarranged in the more severe grades.

5189 THE INTERACTION BETWEEN WALKER TUMOUR CELLS AND MUCOSA CELLS IN THE LAMINA PROPRIA OF GASTRIC MUCOSA IN RATS: THE TUMOUR BEHAVIOUR IN PREVIOUSLY X-IRRADIATED MUCOSA COMPARED TO NORMAL MUCOSA. (Eng.) Broyn, T. (Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo, Norway). *Virchows Arch. [Zellpathol.]* 19(1):27-36; 1975.

One series of 12 rats was exposed to X-irradiation (1500 R) of the stomach 19 days before implantation of Walker tumor cells in the gastric mucosa. The frequency of tumor take and the extent of tumor growth after ten days were compared with a second series with the same tumor implantation, but without X-ray exposure. In a third series simple gastric ulcers without tumor were produced by clamping the gastric wall with a heated (80° C) surgical needle holder. The animals were killed five-seven days later. All the rats were given injections of vinblastine sulfate three hours and ³H-TDR 1 hour before sacrifice. In viewfields with diameter 180 μ the vinblastine-arrested mitoses and labeled cells on the tumor/mucosa border were calculated as percentages of all tumor cells. In the mucosa the total number of proliferating cells was counted at various distances from the border of the tumor or ulcer. No clear differences in the frequency of tumor take and the extent of tumor growth were found between the X-irradiated and the normal rat stomachs, and it is concluded that the X-ray exposure three wks prior to tumor implantation did not reduce the normal mucosal resistance to tumor growth. The percentage of arrested mitoses and labeled cells in the tumor decreased one view field away from the mucosal border, and the number of proliferating cells in the mucosa bordering on the tumors showed a gradual fall with increasing distance up to 0.8-1.0 mm from the tumor border. Within these distances, however, the numbers were much higher than at corresponding distances from the edges of the ulcers. The Walker tumor thus seems to stimulate cell proliferation in mucosa to a much greater extent than a simple ulcer does. The causes of this phenomenon and the possible roles of "chalones" or "anti-chalones" are discussed.

5190 COLONIC CARCINOMA: CLINICOPATHOLOGICAL CORRELATION WITH IMMUNOREACTIVITY. (Eng.)

Pihl, E. (Alfred Hosp., Melbourne, Australia); Hughes, E. S. R.; Nind, A. P. P.; Nairn, R. C. *Br. Med. J.* 3(5986):742-743; 1975.

To study lymphocyte antitumor cytotoxicity, 67 men and 65 women who presented in 1970-1974 with adenocarcinoma of the large bowel were studied. Blood samples were taken immediately before surgery. Autochthonous tumor cells were tested against blood lymphocytes in all 132 cases. Positive cytotoxicity tests were more frequent ($P < 0.01$) in patients with localized tumors (43%) than in those with metastases at initial surgery (17%). Also, cytotoxicity was more frequent ($P < 0.001$) in patients with well-differentiated tumors (64%) than in those with average or poor differentiation (25%). Only four of the 25 patients with well-differentiated tumors had lymph-node metastases, compared to 49 of the 107 with poorly differentiated tumors. Lymphocyte antitumor cytotoxicity may help to maintain tumor differentiation and restrict growth. The positive correlations found in this study are likely to indicate a good long-term prognosis.

5191 GUT BACTERIA AND THEIR METABOLIC ACTIVITIES IN FAMILIAL POLYPOSIS. (Eng.) Bone, E. (Cent. Public Health Lab., London, England); Drasar, B. S.; Hill, M. J. *Lancet* 1(7916):1117-1120; 1975.

The hypothesis that patients with large-bowel cancer can be characterized by the presence of clostridia capable of dehydrogenating the nucleus of steroids and by high fecal bile-acid concentrations was tested by prospectively investigating groups of people with diseases predisposing them to colorectal cancer. Six groups of patients were studied: 1) six affected children of patients with familial polyposis; 2) 13 children of polyposis patients who had not yet developed polyps; 3) 27 patients who had had polyposis earlier and had been treated by colectomy and ileorectal anastomosis; 4) 11 patients treated by colectomy and ileorectal anastomosis for ulcerative colitis; 5) eight patients treated for colonic carcinoma by partial colectomy followed by anastomosis; and 6) three patients with benign polyposis syndromes not thought to predispose to malignancy. Samples of rectal contents collected during sigmoidoscopy were divided into two fractions, one for bacteriological analysis, the other for steroid analysis. Bacteria were isolated and enumerated and lecithinase-negative clostridia were tested for the ability to dehydrogenate the steroid nucleus. Urine samples were assayed for piperidine and pyrrolidine by gas chromatography. Although a high proportion of patients in the first two groups carried clostridia able to dehydrogenate the steroid nucleus, their average rectal bile-acid concentration was low, and only three had characteristics of a high-risk cancer group. The bile acids were generally poorly degraded and were characterized by the presence of chenodeoxycholic acid. In 11 of 19 patients in these two groups, less than 25% of the cholesterol had undergone conversion by the gut flora. In the patients in the third group, rectal bile-acid and neutral-steroid concentrations were low and cholesterol was virtually undegraded. It is suggested that unfavorable intestinal conditions are responsible for the lack of cholesterol degradation in all the

patients with polyposis and in half of those at risk. These findings could lead to the development of a simple diagnostic test if those children of known polyposis patients whose gut flora did not degrade cholesterol subsequently develop the disease.

- 5192 SERUM α -FETOPROTEIN IN THE RELATIVELY EARLY STAGES OF HEPATOCELLULAR CARCINOMA AND ITS RELATIONSHIP TO GROSS ANATOMICAL TYPES. (Eng.) Okuda, K. (Chiba Univ. Sch. Medicine, Chiba, Japan); Kubo, Y.; Obata, H. *Ann. N.Y. Acad. Sci.* 259:248-252; 1975.

Relatively early hepatocellular carcinoma (HCC) was detected by regular serum α -fetoprotein measurements in four men (aged 46-68 yr) with chronic hepatitis or cirrhosis. In two of the patients, the lesion was the solitary type in which a fast-growing tumor forms a major spherical mass with early intrahepatic metastases. Both patients exhibited a very rapid increase in α -fetoprotein and responded to surgery although the mass was 4-6 cm in size. A patient with a well-differentiated HCC of the cirrhotic oligonodular type had low serum α -fetoprotein, which reflected the small mass size (1 x 1 cm). In the fourth patient, the α -fetoprotein level was 175 ng/ml during rapid progression of chronic hepatitis to cirrhosis. Four years later, when celiac angiography revealed a 4 x 4 cm defect, the α -fetoprotein was continuously and mildly elevated. The patient was not autopsied, but his HCC probably fell between the solitary and cirrhotic types. In 212 patients with unequivocal HCC by radioassay, α -fetoprotein was <19 ng/ml in 5.2% and >1000 ng/ml in 80.2%. Among autopsy cases, the frequency of positive α -fetoprotein was significantly higher in patients with solitary and multinodular HCC than in those with the cirrhotic and encapsulated types.

- 5193 PANCREATIC ENDOCRINE TUMORS -- THE RIDDLE OF THEIR ORIGIN AND HORMONE SECRETION. (Eng.) Creutzfeldt, W. (Dept. Medicine, Univ. Göttingen, Göttingen, West Germany). *Isr. J. Med. Sci.* 11(7):762-776; 1975.

The cellular origin of the different pancreatic endocrine tumors is discussed, along with a possible mechanism responsible for their hormone overproduction. Experimental findings do not support the conjecture that these tumors originate from normal pancreatic islets. The growth pattern and the frequent occurrence of tubular and ductular structures in and around pancreatic endocrine tumors suggest that they originate from cells that are not yet differentiated. This assumption is supported by the frequent finding of multiple hormone production, especially in malignant pancreatic endocrine tumors; this finding can be explained only if the tumors originate from protodifferentiated or even predifferentiated cells that specialize during tumor growth. Insulinomas and gastrinomas have both been classified into four ultrastructural types, and two cell types have been found in Verner-Morrison tumors. The only cells found in a considerable number of cases in all pancreatic endocrine tumor types are the type IV of D₁ (undifferentiated stem cell?)

cells. Their occurrence under completely different pathological conditions is compatible with the idea that this cell is a primitive precursor or stem cell which may develop into any cell type of the gastrointestinal endocrine system. The Grimelius silver labeling method appears to label immature endocrine cells in addition to mature A and G cells in different pancreatic tumors and also some epithelial cells of proliferating ducts. Results with this method support the contention that pancreatic endocrine tumors develop from immature precursor cells situated in the ductular epithelium which once protruded from the foregut, and maintains a remarkable regenerative potency. With respect to the mechanism of hormone overproduction by pancreatic endocrine tumors, recent data suggest that decreased storage capacity in some of the tumor cells, resulting in uncontrolled insulin release, is the major defect in insulinomas. The concept of decreased storage capacity as the major defect of insulinoma cells can explain all known clinical, morphological, and biochemical facts, and there is some evidence that this concept can also be applied to other endocrine tumors.

- 5194 CARCINOMA OF THE PANCREAS IN CHRONIC PANCREATITIS. (Ger.) Mohr, P. (Medizinische Universitäts-poliklinik, Kantonsspital, CH-8006 Zurich, Switzerland); Ammann, R.; Largiader, F.; Knoblauch, M.; Schmid, M.; Akovbiantz, A. *Schweiz. Med. Wochenschr.* 105(18):590-592; 1975.

The possible association of chronic pancreatitis and carcinoma of the pancreas was studied. Secondary chronic pancreatitis following carcinoma of the pancreas can be proven histologically in at least 10% of pancreatic cancers. We have followed 146 cases of chronic pancreatitis for an average of 8.7 yr. Two-thirds of our patients show pancreatic calcifications. Our series includes a family with congenital pancreatic insufficiency. So far only one adenocarcinoma of the head of the pancreas has been diagnosed in a 58-yr-old male. Another 57-yr-old man died from a solid metastatic carcinoma, probably of pancreatic origin. During the follow-up period, 2 cancers of the tongue, 2 colonic carcinomas, 2 bladder papillomas, and 1 bronchial and 1 gastric carcinoma were found in eight patients. Carcinoma of the pancreas probably does not occur more frequently in chronic non-hereditary pancreatitis than in the average population. A review of the literature suggests that there may be a higher incidence of carcinoma in families with hereditary chronic pancreatitis. As pancreatic carcinoma is rare in chronic pancreatitis there is no reason for early aggressive surgery, e.g. pancreatectomy, in these patients.

- 5195 TRYPTOPHAN URINARY BLADDER ABSORPTION AND BLADDER CANCER. (Eng.) Flanagan, M. J. (Rush-Presbyterian-St. Luke's Medical Center, Chicago, Ill. 60612); Ekbal, S.; Coogan, P. S.; Kalin, G.; Hass, G. M. *Invest. Urol.* 13(1):17-19, 1975.

A continuous dietary regime containing 0.24% 2-acetylaminofluorene (2-AAF) was administered to rabbits; urothelial papilloma and carcinoma were found

in about 40% of those surviving 2 yr. The urinary bladder absorption of tryptophan by male rabbits after 12 mo on the diet containing 2-AAF was 33% in those rabbits that developed gross tumor, compared to 15% in those that did not. Tryptophan absorption averaged 11.7% in 3 patients with no history of urothelial cancer, 6.5% in 8 who had documented urothelial cancer resected previously, and 39.5% in 5 patients who had bladder tumors at the time of study. In two of these latter patients, absorption was <2% after transurethral resection. The tumors in the 5 patients were only a few mm in diameter. Unusually high absorption might provide a method for selective exposure to antineoplastic agents. Absorption by the urinary bladder may play a critical role in urothelial carcinogenesis.

- 5196 MORPHOGENESIS OF ELASTOTIC TRANSFORMATION OF BREAST CANCER STROMA. (Ger.) Kozłowski, H. (Frauenklinik der Medizinischen Akademie Gdansk, Gdansk, ul. Kliniczna 1, Poland); Hrabowska, M. *Arch. Geschwulstforsch.* 45(2):163-172; 1975.

In 50 biopsy specimens of breast carcinoma and 21 autopsy samples the characteristic finding was multifocal elastotic transformation of collagen bundles devoid of mucopolysaccharide. The fields of degenerated connective tissue had the capacities to dye like elastic fibers. The increase of elastotic material in stroma of breast cancer may be associated with the collagen degradation caused by metabolites of cancer tissue. The phenomenon occurred in all age groups and was not closely associated with the grade of histological malignancy.

- 5197 BULK TRANSFER OF FLUID IN THE INTERSTITIAL COMPARTMENT OF MAMMARY TUMORS. (Eng.) Butler, T. P. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Grantham, F. H.; Gullino*, P. M. *Cancer Res.* 35(11/Part 1):3084-3088; 1975.

Evidence is presented to show that convective currents in tumor interstitial spaces exist, that an estimate of their magnitude can be obtained experimentally and that this estimate is not substantially changed during hormone-dependent tumor regression. Venous blood leaving a solid tumor showed higher erythrocyte concentration than did aortic blood. Net fluid loss of efferent blood as calculated from hematocrit differences was 2.7-6.7% of flow volume, 4.5-10.2% of perfusing plasma volume, or 0.14-0.22 ml fluid/hr/g in 2-5 g transplanted MTW9 and Walker 256 mammary carcinomas, and primary *N*-nitrosomethylurea- and 7,12-dimethylbenz(a)anthracene-induced mammary carcinomas of rats. Net fluid loss was directly related to blood flow but inversely related to tumor size. Increased hydrostatic pressure in tumor interstitial space was a consistent finding. Micropore chambers embedded in transplanted tumors drained 4-5 times more interstitial fluid than did identical chambers in the sc tissue. It is concluded that convective currents are present within the interstitial spaces of tumors, that the magnitude of fluid transfer can

be measured by the difference in hemoconcentration between afferent and efferent tumor blood, and that the volume of this fluid transfer is not altered by hormone-induced tumor regression. The increased hydrostatic pressure of tumor interstitial spaces is interpreted as being due to absence of an anatomically well-developed lymphatic network. The bulk transfer of fluid within interstitial spaces is comparable to lymphatic drainage and should be considered in assessing drug concentration and distribution in solid tumors.

- 5198 MULTIPLE PRIMARIES AND GYNECOLOGIC MALIGNANCIES. (Eng.) Buchler, D. A. (Univ. Wisconsin Medical Center, Madison, Wis. 53706). *Am. J. Obstet. Gynecol.* 123(4):376-381; 1975.

The frequency and types of multiple primary malignancies found in patients with gynecologic malignancies over a 13-yr period are reviewed. Additional primary malignancies were most frequently associated with the ovary (9.3%), cervix (8.9%), corpus (7.7%), and vulva (6.3%). Fifty percent of the multiple primary malignancies occurred prior to the presenting gynecologic cancer, while 3% were found simultaneously. Among the 209 patients with multiple cancer, patients with cervical primaries had the greatest number of second malignancies. The major extragenital sites of additional malignancies were the breast (28%), and colon (14%). Seventy-five percent of the breast tumors were noted to have occurred prior to the development of the genital tract malignancy; 74% were associated with primaries of the corpus or ovaries. Great variation was noted in the time interval between the genital tract cancer and development of subsequent malignancies. However, 41% of the cervical cancer patients developed the second malignancy more than 10 years after treatment. Of 77 patients found developing subsequent malignancies, 61% initially had carcinoma of the cervix; those developing a vulvar or cervical carcinoma survived most frequently. Mortality in 50% of patients with subsequent breast and colon malignancy could be attributed to either their primary disease or an unrelated problem.

- 5199 CARCINOMA OF THE OVARY. (Ger.) Engeler, V. (Universitäts-Frauenklinik Zurich, Switzerland). Berchtold, H.; Studer, H. J. *Adv. Obstet. Gynaecol.* 53:1-116; 1974.

Observations on 568 patients with ovarian cancer treated during 1950-1971 are reported; also the relevant literature is reviewed. The frequency of this cancer increased after age 40 and was maximum for the ages 50-59 yr. In this series, 42% of the women were childless.

- 5200 SUPERIOR GROWTH OF THE RIGHT GONAD IN HUMAN FOETUSES. (Eng.) Mittwoch, U. (Dept. Human Genetics, University Coll. London, Wolfson House, Stephenson Way, London NW1 4HE, U.K.); Kirk, D. *Nature* 257(5529):791-792; 1975.

To study possible asymmetry, right and left gonads, from therapeutically aborted human fetuses (14 males, 9 females) were compared. The right gonad was 5% greater in fresh weight, and 7-8% greater than the left in total protein and total DNA when the results for males were averaged. The corresponding results for females were 18%, 20%, and 14%, respectively. This increased growth rate of the right gonad may explain the greater risk of some gonadal tumors on the right side.

- 5201 MULTIPLE ENDOCRINE ADENOMATOSIS TYPE IIB: DIAGNOSIS AND TREATMENT. (Eng.) Block, M. B. (Medical Librarian, Fitzsimons Army Medical Center, Denver, Colo. 80240); Roberts, J. P.; Kadair, R. G.; Seyfer, A. E.; Hull, S. F.; Nofeldt, F. D. *J.A.M.A.* 234(7):710-714; 1975.

A case of multiple endocrine adenomatosis type IIB (MEAIIB) was described in detail. A 29-yr-old man with a marfanoid habitus, peculiar mucosal neuromas of the lips and tongue, high arched palate, hyperplastic corneal nerves, and hypertension was found at operation to have medullary carcinoma of the thyroid, parathyroid hyperplasia, and pheochromocytoma. These symptoms and findings are characteristic of MEAIIB syndromes. Treatment consisted of bilateral adrenalectomy and thyroid-parathyroid surgery, followed by hormone replacement therapy. The patient's relatives were contacted for prompt screening of asymptomatic individuals by measurement of basal catecholamine excretion and serum calcitonin levels.

- 5202 THE FINE STRUCTURE OF THYMOMA, WITH EMPHASIS ON ITS DIFFERENTIAL DIAGNOSIS: A STUDY OF TEN CASES. (Eng.) Levine, G. D. (Stanford Univ. Medical Center, Stanford, Calif. 94305); Rosai, J.; Bearman, R. M.; Polliack, A. *Am. J. Pathol.* 81(1):49-86; 1975.

Ten thymomas were examined under the electron microscope to provide a basis for comparison with other thymic tumors. The patients included eight women and two men, aged 14-72 yr. As in the normal thymus, epithelial cells exhibited many well-formed desmosomes, thick branching tonofilaments, basal lamina, and elongated cytoplasmic processes. These ultrastructural characteristics support the definition of a thymoma as a neoplasm arising from the epithelial-reticular cell of the normal thymus. They proved useful in the differential diagnosis of thymoma from a variety of anterior mediastinal tumors including thymic carcinoid, lymphoma, germinoma (seminoma type), and fibrous mesothelioma. Lymphocytes showed a variable morphology, presumably reflecting the phase of the cell cycle at time of examination. In five cases, transformation was evidenced by moderate development of the nucleolonema, increased euchromatin, electron lucency of mitochondria, and an increase in cytoplasmic polyribosomes. Mitoses were numerous in four of these five cases and there was also a high lymphocyte death rate, with the resulting phagocytosis by macrophages producing a starry-sky appearance. This pattern is present microscopically in 25% of thymomas and does not necessarily reflect a malignant lymphoma.

Three of the patients with a high lymphocyte mitotic rate were apparently cured by surgery. In four cases, occasional epithelial cells contained many vacuoles and in one case epithelial vacuoles contained degenerating lymphocytes. The occurrence of such emperipolesis is rare in thymoma. Although long-spacing collagen was found in the perivascular space in four cases, this is also seen in the normal and hyperplastic thymus and is therefore not of diagnostic value. Cystic gland-like spaces observed in two cases contained no dense-core granules and did not appear adapted to secretory function. It is concluded that electron microscopy is an invaluable aid in the differential diagnosis of thymomas when light microscopic studies are equivocal or controversial.

- 5203 DIFFERENTIAL CHARACTERIZATION OF THE "RETICULUM CELL" IN LYMPHORETICULAR NEOPLASMS. (Eng.) Yam, L. T. (Scripps Clin. Res. Found., La Jolla, Calif.); Tavassoli, M.; Jacobs, P. *Am. J. Clin. Pathol.* 62(2):171-179; 1975.

Several diseases involving reticulum cells, poorly differentiated hemopoietic cells and histiocytes were studied in a combined morphological and cytochemical approach to establish a differential characterization of the cells involved in these reticulum cell diseases. Cases studied included: histiocytic lymphoma, 10; poorly differentiated lymphocytic lymphoma, 10; acute myelomonocytic leukemia, 10; leukemic reticuloendotheliosis, 10; and one case of Sjogren's syndrome with histiocytic lymphoma (immunoblastic sarcoma). The cytochemical markers used were: chloracetate esterase for neutrophilic granulocytes, nonspecific esterase and fluoride-resistant esterase for monocytes and histiocytes (phagocytes); tartrate-resistant acid phosphatase for the reticulum cells of leukemic reticuloendotheliosis; and pyronin for the lymphatic reticulum cells (germinal center cells). Monocytes predominated in acute monocytic leukemia. They were phagocytic and characterized by strong activity of nonspecific esterase. Immature granulocytes seen predominantly in acute granulocytic leukemia had strong activity of chloracetate esterase but very weak or no activity for nonspecific esterase. Hairy cells were pathognomonic for leukemic reticuloendotheliosis; they had a hairy appearance, strong tartrate-resistant acid phosphatase activity, and usually insignificant activity of esterases. The lymphatic reticulum cells that predominated in cases of histiocytic lymphoma were morphologically similar to the lymphatic reticulum cells of Moeschlin and to completely transformed lymphocytes stimulated by phytohemagglutinin. The lymphoblasts and atypical lymphocytes often seen in poorly differentiated lymphocytic lymphomas had no positive cytochemical markers. It is concluded that a combined morphologic and cytochemical approach can improve the identification and definition of the cells of the various lymphoreticular neoplasms. With the addition of immunocytochemical methods and by the use of functional criteria for the cells, it should be possible to provide objective means to identify the various types of

cells and to classify this group of reticulum-cell neoplasms with improved precision.

5204 GAUCHER'S DISEASE ASSOCIATED WITH CHRONIC LYMPHOCYTIC LEUKAEMIA, GOUT AND CARCINOMA.

(Eng.) Chang-Lo, M. (Mount Sinai Hosp. Medical Center, Chicago, Ill.); Yam, L. T.; Rubenstone, A. I.; Schwartz, S. O. *J. Pathol.* 116(4):203-207; 1975.

Both Gaucher's disease and chronic lymphocytic leukemia were diagnosed in a 75-yr-old man who subsequently developed gout and a carcinomatous polyp of the sigmoid colon. The original diagnoses were established by typical blood and bone marrow findings of chronic lymphocytic leukemia, the demonstration of Gaucher cells in the marrow aspirates, and the presence of Gaucher cells in the excised spleen and liver biopsy seven years before death. The Gaucher cells were more numerous in the liver biopsy than in the liver at autopsy. At the time of death, the bone marrow was almost replaced by lymphocytes and Gaucher cells, confirming the original diagnoses. The original lymph node examined showed no Gaucher cell infiltration; at autopsy, however, the lymph nodes were involved. There was no evidence at autopsy of residual carcinoma from the polypectomy performed four yr previously, but a sessile adenomatous polyp was found in the ascending colon and a pedunculated adenomatous polyp in the sigmoid colon. Although this is the first reported case of Gaucher's disease associated with chronic lymphocytic leukemia, the association may not be coincidental. Both entities are diseases of the reticuloendothelial system and therefore may share a common etiological factor.

5205 MALIGNANT LYMPHOMA OF CONVOLUTED LYMPHOCYTES: A NEW ENTITY OF POSSIBLE T-CELL TYPE. (Eng.) Barcos, M. P. (Dept. Pathology, Roswell Park Memorial Inst., Buffalo, N.Y. 14263); Lukes, R. J. *Prog. Clin. Biol. Res.* 4:147-178; 1975.

Twenty-seven cases of a lymphoproliferative disorder of distinctive lymphocytes with convoluted nuclei are described, and they appear to represent a distinctive clinical morphologic entity. These patients had a median age of 13, a male/female sex ratio of 2:1, and a median survival of ten months. Twenty patients presented with a prominent mediastinal mass, six with respiratory obstruction, and eight with pleural effusion. Eleven patients had leukemic bone marrow involvement at diagnosis, and nine developed leukemia subsequently. Morphologically, the cellular proliferation was characterized by widely infiltrating and poorly differentiated appearing, noncohesive cells with scanty nonpyroninophilic cytoplasm, primitive appearing chromatin, small nucleoli, numerous mitoses, a distinctive convoluted nucleus, and a spectrum of cell size ranging from that of a small lymphocyte to that of a reactive histiocyte nucleus. The striking mediastinal presentation resulting from the proliferation of the distinctive convoluted lymphocytes, the frequent sparing of the follicular centers in lymph nodes, the marked sensitivity to steroid or radiation

therapy, and the recent reports of E-binding cells in association with childhood mediastinal lymphomas suggest that the class of malignant lymphoma described here represents a T-cell lymphoproliferative disorder. The pubescent age group and the striking male preponderance suggest that hormonal imbalance may play a role in its pathogenesis.

5206 THE HISTOPATHOLOGY OF MALIGNANT LYMPHOMA.

(Eng.) Lennert, K. (Dept. Pathology, Univ. Kiel, 2300 Kiel, Postfach 43 24, West Germany); Mohri, N.; Stein, H.; Kaiserling, E. *Br. J. Haematol.* 31(Suppl.):193-203; 1975.

A reclassification of non-Hodgkin's malignant lymphomas is presented based on advanced immunological techniques, cytological and cytochemical techniques and electron microscopy. The terminology used is that of the Kiel Classification devised after the Lymphoma Conference in London, October 1973. Lymphomas of low-grade malignancy are classified in four categories: (1) Lymphocytic - includes (a) chronic lymphocytic leukemias of the B-cell type which give a negative PAS reaction (b) hairy cell leukemias which probably are neoplasias of a subgroup of B-lymphocytes; lymphoblasts do not occur (c) Sezary syndrome and mycosis fungoides (d) lymphocytic lymphomas of the T-cell type, also known as chronic lymphocytic leukemias of the T-cell type; (2) Lymphoplasmacytoid (Immunocytic) - mainly B-lymphocytes with PAS positive inclusions granules; (3) Centrocytic - consists of small to medium-sized germinal center cells (germinocytes); (4) Centroblastic-Centrocytic - consists mainly of centrocytes and a small to moderate number of centroblasts (germinoblasts). Malignant lymphomas are assigned to three categories: (1) Centroblastic - tumor represents the anaplastic end phase of follicular lymphoma and was previously known as reticulosarcoma; (2) Lymphoblastic - includes all acute lymphatic leukemias of childhood, Burkitt's type lymphomas and lymphomas of the convoluted cell type (acid-phosphatase type); (3) Immunoblastic - from transformed B-lymphocytes and tissue homogenates have high immunoglobulin content. Apparently, most non-Hodgkin's lymphomas are derived from the B-lymphocyte system. Only some lymphocytic and lymphoblastic and a very few immunoblastic lymphomas originate from the T-lymphocyte system. Epidemiological data on the incidence of malignant lymphomas in northern West Germany is included and shows that after Hodgkin's Disease, which accounts for more than half the cases, the centroblastic-centrocytic type is most frequent.

5207 NON-HODGKIN'S LYMPHOMA IN CHILDREN: A REVIEW OF 104 CASES. (Eng.) Wollner, N. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Burchenal, J. H.; Exelby, P.; Lieberman, P. H.; D'Angio, G.; Murphy, M. L. *Prog. Clin. Biol. Res.* 4:179-223; 1975.

Between 1964 and 1974, 104 children with non-Hodgkin's lymphoma were followed and studied for the following reasons: (a) to determine the frequency of various primary sites, staging and histology, and the clinical course and survival associated with

each of these parameters; (b) to determine the prognostic relevance of old and new histological classifications; (c) to determine what factors, if any, hold prognostic value; (d) to analyze three different modes of therapy and their influence on survival; and (e) to introduce a therapy for treatment of non-Hodgkin's lymphoma for all stages -- the LSA₂-L₂ protocol -- and to demonstrate its rationale in the light of previous treatment results. Of the 104 children studied, 43 were included in the LSA₂-L₂ protocol. Of the patients on this regimen, 37 (84%) were still alive on January 31, 1974. Of these 37, 35 had no evidence of disease for 3-34 mo from diagnosis. The median observation time was greater than 16 mo, far beyond the danger period for the other protocols. Seventy-seven of these patients had far advanced disease (stages III and IV), and 44% had initial bone marrow involvement. In this latter group 68% also had peripheral blood involvement. Eighty-six percent of the patients had Rappaport's diffuse histological variety, which has long been considered a poor prognostic sign. The intensive LSA₂-L₂ multidisciplinary approach has greatly improved the outlook for this previously fatal disease, with its early recurrences and death.

- 5208 THE PLATELETS IN PRELEUKEMIA AND MYELOMONOCYTIC LEUKEMIA: ULTRASTRUCTURAL CYTOCHEMISTRY AND CYTOGENETICS. (Eng.) Maldonado, J. E. (Mayo Clinic, Rochester, Minn.); Pierre, R. V. *Mayo Clin. Proc.* 50(10):573-587; 1975.

Light and electron microscopic studies of platelets from 16 patients with myelomonocytic leukemia or "preleukemia" were undertaken. Major morphologic alterations in 15 and minor ones in one patient were observed. Although variable in severity from case to case, the changes present followed a distinct pattern. In most cases there were two platelet populations, one morphologically normal and one morphologically abnormal. The most salient changes pertained to size (giant forms), shape (the platelets being rounded and probably spheroidal), decrease or absence of the microtubules, and increase in immature elements. A striking feature was the variation in size and shape of the granules, with truly giant forms (up to 2.5 μ m) being present. In cytogenetic studies in 14 cases, there was no correlation between the chromosomal changes and the various types of platelet anomalies.

- 5209 CYTOPHOTOMETRIC AND CYTOGENETIC STUDIES OF PROLACTIN-SECRETING TRANSPLANTABLE PITUITARY TUMOR CELLS IN C57BL MICE. (Eng.) Hoshino, K. (Faculties of Medicine and Dentistry, Univ. Manitoba, Manitoba, Canada); Ray, M.; Ward, E. *Acta Cytol. (Baltimore)* 19(4):337-341; 1975.

The fifth generation pituitary tumor of a C57BL/6J female mouse was used for cytophotometric and cytogenetic analyses. Feulgen-coriphosphine O and galloxyaniline chrome alum stainings were used for DNA and total nucleic acid. The DNA and total nucleic acid contents in tumor cells were 3136 and 5207 U, respectively, compared to 1982 and 2615 U respectively in normal pituitary cells. The total

nucleic acid content in tumor cells had a much greater spread than the DNA content alone, and the DNA:total nucleic acid ratio was below normal, indicating that RNA was increased in tumor cells. Cytogenic analysis showed that this tumor had cells with 39, 40 and 41 chromosomes. The cells with 39 and 41 (including one centric fragment) chromosomes could not be karyotyped. Among the cells having 40 chromosomes, few cells showed similar abnormal karyotype which included trisomic 8, monosomic X and most likely a partial long arm deletion of chromosome 16. This approach might establish a correlation between karyotypic evolution and the DNA/RNA content of neoplastic cells.

- 5210 NORMAL GENETICALLY MOSAIC MICE PRODUCED FROM MALIGNANT TERATOCARCINOMA CELLS. (Eng.) Mintz, B. (Inst. Cancer Res., Fox Chase, Philadelphia, Pa. 19111); Iilmensee, K. *Proc. Natl. Acad. Sci. USA* 72(9):3585-3589; 1975.

Malignant mouse teratocarcinoma (or embryonal carcinoma) cells with a normal modal chromosome number were taken from the "cores" of embryoid bodies grown only *in vivo* as an ascites tumor for eight years. The cells were injected into blastocysts bearing many genetic markers in order to test the developmental capacities, genetic constitution, and reversibility of malignancy of the core cells. Ninety-three live normal pre- and postnatal animals were obtained. Of 14 analyzed, three were cellular genetic mosaics with substantial contributions of tumor-derived cells in many developmentally unrelated tissues, including some never seen in the solid tumors that form in transplant hosts. The tissues functioned normally and synthesized their specific products (e.g., immunoglobulins, adult hemoglobin, liver proteins) coded for by strain-type alleles at known loci. In addition, a tumor-contributed color gene, *steel*, not previously known to be present in the carcinoma cells, was detected from the coat phenotype. Cells derived from the carcinoma, which is of X/Y sex chromosome constitution, also contributed to the germ line and formed reproductively functional sperms, some of which transmitted the *steel* gene to the progeny. After almost 200 transplant generations as a highly malignant tumor, embryoid body core cells appear to be developmentally totipotent and able to express, in an orderly sequence in differentiation of somatic and germ-line tissues, many genes hitherto silent in the tumor of origin. This experimental system of "cycling" teratocarcinoma core cells through mice, in conjunction with experimental mutagenesis of those cells, may therefore provide a new and useful tool for biochemical, developmental, and genetic analyses of mammalian differentiation. The results also furnish an unequivocal example in animals of a non-mutational basis for transformation to malignancy and of reversal to normalcy. The origin of this tumor from a disorganized embryo suggests that malignancies of some other, more specialized, stem cells might arise comparably through tissue disorganization, leading to developmental aberrations of gene expression rather than changes in gene structure.

5211 SEQUENTIAL MORPHOLOGICAL STUDY OF TERATOMAS DERIVED FROM DISPLACED YOLK SAC.

(Eng.) Sobis, H. (Rega Inst., Univ. Leuven, Belgium); Vandeputte, M. *Dev. Biol.* 45(2):276-290; 1975.

The sequential histological and ultrastructural morphology of benign teratomas derived from displaced visceral yolk sacs was studied and compared with normal embryogenesis and with the development and differentiation of experimental teratocarcinomas. Twelve days after the mating of inbred Wistar albino strain R rats, fetuses were removed from both uterine horns together with the amnion. After fetectomy, the visceral yolk sac was pulled through the incision and left outside the uterine wall. The animals were killed at 2- to 7-day intervals from the second to the 60th day after fetectomy. The whole uterus was fixed in formol for histological examination. For electron microscopy, one tumor from each rat was fixed in glutaraldehyde and post-fixed in osmium tetroxide. Serial sections cut from paraffin blocks were stained with erythrosin-hematoxylin. Thin sections were stained with lead hydroxide. The first signs of proliferation of endodermal cells were seen four days after fetectomy. Some endodermal cells undergoing progressive degeneration were seen at day 6, while most of the cells divided and formed multilayered endodermal epithelium. At day 8, the formation of glandular structures began; at day 10, the gut with all its layers appeared. At day 13, pancreatic tissue developed in the mesenchymal tissue surrounding the intestine. The appearance of structures of endodermal origin in the yolk sac-derived tumors had the same sequence as in normal embryogenesis. These observations suggest that the 12-day-old extra-embryonic endoderm retains a capacity of differentiation similar to that which characterizes the embryonic endoderm at an earlier stage of pregnancy. The proliferation of mesenchymal cells in the displaced visceral yolk sac started at day 4 after fetectomy and showed differentiation into cartilage two days later. The formation of cartilage in the yolk sac-derived tumors at days 6, 8, and 10 was similar to the chondrogenesis previously described in the rat embryo between 12-16 days of gestation. Twenty-two days after fetectomy, several tumors attached to the uterine wall reached 1 cm in diameter. These tumors showed the presence of such tissues as skin with its appendages, cartilage, bone, bone marrow, adipose tissue, striated muscle and mucous glands. These observations make the theory of a germ cell origin for the yolk sac-derived teratomas unlikely. Another explanation for the presence of different tissues, including ectodermal tissues, in the teratomas derived from the visceral yolk sac, is that at a certain stage of development the cells of every germ layer can give rise to various structures.

5212 MALIGNANT LYMPHOMA RESEMBLING BURKITT'S TUMOUR IN RHESUS MONKEYS (LIGHT- AND ELECTRON MICROSCOPIC STUDIES). (Eng.) Schneider, P. (Abt. Experimentelle Pathologie, D-795 Biberach (Riss), West Germany). *Beitr. Pathol.* 155(3):285-296; 1975.

Three proven cases of spontaneous lymphomas resembling Burkitt's tumor in immature Rhesus monkeys were studied. Serological and virological tests were performed, and the affected tissues were examined grossly and by light and electron microscopy. All of the affected animals had tumors of both the retroperitoneum and lymph nodes. The ovaries and uteri of the two females showed tumor tissue as did the liver of the male monkey; the main parenchyma tissues and spleen were unchanged. Light microscopy of the tumors revealed a uniform overgrowth of lymphoblastic and lymphoid cells; uniformly interspersed macrophages with abundant clear cytoplasm containing cell debris, large lipid droplets, and PAS-positive granular material gave the tumor a characteristic "starry sky" appearance. A marked cytoplasmic pyroninophilia that could be abolished by prior digestion with ribonuclease was histochemically demonstrable in all tumor cells. Only one monkey showed tumor cell infiltrations in the liver, spleen, and kidneys. Electron microscopy showed the tumor cells to be lymphoblasts of about 8 μ in diameter. They contained round or oval, occasionally deeply indented cell nuclei with relatively clear interchromatinic substance; mostly well-developed nucleoli; sparse rough endoplasmic reticulum; large numbers of free ribosomes and polyribosomes; a few large, bizarre mitochondria, often situated at one pole; and, in some cells, lipid vacuoles. The characteristics of these tumors correspond to those of Burkitt's lymphoma in humans, the former being classified as an undifferentiated malignant lymphoma. Tumor cell cultures have revealed virus particles, the morphological, serological, and biochemical nature of which is presently being characterized.

5213 ALVEOLAR SOFT PART SARCOMA: AN ELECTRON MICROSCOPIC STUDY. (Eng.) Unni, K. K. (Mayo Clinic, Rochester, Minn.); Soule, E. H. *Mayo Clin. Proc.* 50(10):591-598; 1975.

Three samples of alveolar soft part sarcomas (from two patients) were studied with the electron microscope. Polygonal cells were found arranged in a glandular pattern surrounded by an incomplete basement membrane. Many of the cells contained membrane-bound rhomboid crystals and secretory granules. On the other aspect of the basal lamina, or rarely within, there were spindle cells with sparse organelles. There was a rich network of capillaries between clusters of tumor cells. These features are similar to those found in normal carotid bodies and chemodectomas. This suggests that alveolar soft part sarcomas arise from paraganglia.

5214 FINE STRUCTURAL COMPARISON OF EWING'S SARCOMA WITH NEUROBLASTOMA. (Eng.) Nakayama, I. (Nagasaki Univ. Sch. Medicine, Nagasaki, Japan); Tsuda, N.; Muta, H.; Fujii, H.; Tsuji, K.; Matsuo, T.; Takahara, O. *Acta Pathol. Jpn.* 25(3):251-268; 1975.

Two cases of Ewing's sarcoma (20-mo-old girl, 18-yr-old boy) and two of neuroblastoma (32-mo-old girl, 20-mo-old boy), rosette forming and round cell type, were studied electron microscopically.

The neoplastic cells of Ewing's sarcoma were characterized by aggregated glycogen particles in the cytoplasm. They had pseudopod-like cytoplasmic processes having tight junctions, which never contained microtubules or mitochondria. Ewing's sarcoma cells seemed to be at different stages of maturation. Some cells possessed a large amount of smooth and rough endoplasmic reticulum, large Golgi complexes and numerous phagosomes containing glycogen particles as well as cytoplasmic organelles and were considered more mature. The neoplastic cells of neuroblastoma, rosette forming type, were characterized by synaptic junctions and numerous cytoplasmic processes with production of neurites containing microtubules, neurofibrils, mitochondria and a few catecholamine granules. A few cytoplasmic processes containing mitochondria were observed even in the round cell type. These two types of tumor can be easily distinguished by electron microscopy.

- 5215 CENTRAL NEUROBLASTIC TUMOUR ASSOCIATED WITH SMOOTH MUSCLE FIBERS. A STUDY IN THE OPTIC AND ELECTRON MICROSCOPES. (Eng.) Vuia, O. (Inst. Neuropathology, Justus-Liebig-Univ., Giessen, West Germany); Hager, H. *Eur. Neurol.* 13(3):258-272; 1975.

A microcystic intraspinal tumor in a four-yr-old girl was studied. The histologic examination showed neuroblastic elements developing next to smooth muscle fibers. The tumor had diffusely invaded the meninges, presenting a marked collagen reaction. Ultrastructurally, the neuroblastic elements exhibited an arrangement proper to the neural tube. The presence of osmiophil neurosecretory dense-core vesicles and microtubuli also indicate the neuroblastic nature of this tumor. The smooth muscle fibers contained microfibrils and were delimited by a basement membrane. The muscular fibers were visibly in contact with the blood vessels. These aspects demonstrate that this medullomyoblastoma is a malignant bidermal teratoid tumor of the CNS. Dysgenesis of the ectomesenchyma may be considered to be the basis of the development of this type of tumor. The association of this tumor with muscle fibers implies neuroectodermal and mesodermal participation during its development.

- 5216 FINE STRUCTURAL STUDY OF CHORDOMA. (Fre.) Tripier, M. F. (Laboratoire de Neuropathologie, Faculte de Medecine, 27 Bd J. Moulin, 13385 Marseille, Cedex 4, France); Hassoun, J.; Toga, M. *J. Neurol. Sci.* 25(3):361-370; 1975.

An ultrastructural study of a sacral chordoma in a 65-yr-old woman is presented. The woman was hospitalized because of sciatic pain of 20 yr duration and constipation and urine retention commencing 4 mo prior to admission. A multilobular, smooth-surfaced mass, 12 cm in diameter and of a gelatinous consistency was excised. To prepare the specimen for study by electron microscopy, it was fixed in a 5% solution of glutaraldehyde in Millonig phosphate buffer for 1 hr and then in 1% osmic acid for 1 hr. Ultrastructurally, the tumor cells appeared to have

similar constant characteristics. Large nucleoli and numerous nuclear bodies indicating cell hyperactivity were visible in the nucleus. In the perikaryon there were tonofibrils, glycogen particles, neutral lipids, and ergastoplasmic sacs. Tonofibrils were the most widely distributed organelles and have been observed in all literature reports of chordomas. On contact with cell membranes, they formed bundles and connected with the desmosomes. These specialized cell junctions indicate the epithelial origin of the neoplastic cell. Sacs associated with the rough endoplasmic reticulum and the mitochondria were observed in all tumor cells. Rare giant cells interpreted by other authors as "physaliphorous cells" are considered rather to correspond to interstitial histiocytic macrophages. Vacuoles described by others as intracytoplasmic are actually invaginations into the tumor cell cytoplasm of mucopolysaccharide material associated with the abundant interstitial histiocytes.

- 5217 ADHESION OF MALIGNANT AND NONMALIGNANT CELLS TO CULTURED EMBRYONIC SUBSTRATES. (Eng.) de Ridder, L. (Clinic for Radiotherapy and Nuclear Medicine, Akademisch Ziekenhuis, De Pintelaan 135, 9000 Ghent, Belgium); Mareel, M.; Vakaet, L. *Cancer Res.* 35(11/Part 1):3164-3171; 1975.

Experiments in tissue culture fragments and living substrates *in vitro* were used to study adhesion. Malignant HeLa, hepatoma, and PY cells, as well as nonmalignant BHK cells, were transplanted into cultured chick blastoderms and organ fragments from chick embryos. Adhesion was evaluated by time-lapse cinematography, by flushing with Tyrode's solution, and by histological examination after fixation. It was shown that the adhesion of these tissue culture fragments depends on the nature of the substrate. Substrates of connective tissue, mesenchyme, and the basal side of epithelia proved to be adhesive. In contrast, the apical side of intact epithelia was nonadhesive. Perforated epithelia allowed adhesion at the site of the perforation. In the presence of dilysine, HeLa cells adhere to the apical side of epithelia and to the dorsal side of the upper layer of the blastoderm. It was concluded that that apical side of intact epithelia constitutes an inappropriate substrate for adhesion of a large variety of cells, *in vitro* as well as *in vivo*. Alteration of this characteristic in the presence of dilysine indicates that long-range electrostatic repulsion might be responsible for the nonadhesive character of the epithelia.

- 5218 EFFECTS OF CIGARETTE SMOKE ON THE BRONCHIAL EPITHELIUM OF SYRIAN HAMSTERS: ULTRASTRUCTURAL STUDIES. (Eng.) Reznik-Schuller, H. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Weichert-Allee 9, 3000 Hannover-Kleefeld, West Germany); Reznik, G.; Mohr, U. *J. Natl. Cancer Inst.* 55(2):353-369; 1975.

The fine structural changes in the bronchial epi-

thelium of Syrian hamsters after chronic smoke exposure were studied. Male and female 12-wk-old Syrian hamsters were exposed to total smoke of two types of unfiltered research cigarettes. For one type, the smoke delivery per 30 cigarettes of mainstream total particulate matter reaching the exposure chamber was 320.27 mg. Nicotine (2.96 mg), dry condensate (37.2 mg), and CO (3.5 g/100 mg) were delivered per cigarette. The second type of cigarette had a delivery of 93.12 mg mainstream total particulate matter per 30 cigarettes; corresponding exposure values were 0.5 mg nicotine, 12.3 dry condensate, and 5.32 g/100 mg CO delivered per cigarette. Animals were exposed once a day, five days a week for 12 mo, then sacrificed. Ten samples of lobar or segmental bronchi were excised from each lung and microscopically studied. While the bronchial epithelia of all control hamsters remained unaltered, that of all animals exposed to smoke were hyperplastic. It consisted of up to seven rows of proliferating basal cells, ciliated and nonciliated cells, areas of tilted nuclear axes, and invaginations. There were exceptionally large lysosomes (1.7 μ) in many epithelial cells, and many large, ovoid, multivesiculated bodies located in nonciliated and basal cells. Both ciliated and nonciliated cells contained whorl-like membranous structures and electron-dense structures. Early stages of squamous metaplasia were sporadic, and no bronchogenic tumors were found. The alterations neither reversed nor advanced one year after smoking was terminated. It is concluded that in hamsters the response of the bronchial epithelium to smoke exposure does not depend on the amount of mainstream total particulate matter and condensate of the cigarettes.

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- 5270 UTERINE TUMORS OF MESENCHYMATOUS ORIGIN. PROBLEM OF THEIR DEFINITION AND CLASSIFICATION. (Fre.) Van Bogaert, L.-J. (Laboratoire

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5273 ELECTRON MICROSCOPY OF PITUITARY TUMORS OF MICE OF THE T. M. STRAIN [abstract]. (Eng.) Szepesenwol, J. (Dept. Anatomy, Univ. Montreal, Canada); Stephens, H.; Boschetti, N. V.; Sandborn, E. B. *Proc. Am. Assoc. Cancer Res.* 16:76; 1975.

5274 PENETRATION OF AN ASCITIC RETICULUM CELL SARCOMA OF THE GOLDEN HAMSTER INTO THE BODY WALL AND THROUGH THE DIAPHRAGM: A SCANNING ELECTRON MICROSCOPIC (SEM) STUDY. (Eng.) Lunsken, C. (Inst. Pathology, Univ. Zurich, Switzerland); Strauli, P. *Virchows Arch. [Zellpathol.]* 17(3):247-259; 1975.

5275 IS ZOSTER A SIGN OF UNDIAGNOSED CANCER? (Swe.) Molin, L. (Regional Hosp., S-581 85 Linkoping, Sweden). *Lakartidningen* 72(11):1087-1088; 1975.

5276 PRIMARY TUBAL CARCINOMA RESEMBLING TUBERCULOSIS INFLAMMATION. (Pol.) Krasnodebski, J. (Instytut Ginekologii i Poloznictwa, ul. Batorego 15. 41-902 Bytom., Poland); Poreba, R. *Wiad. Lek.* 28(7):601-602; 1975.

See also:

- * (Rev): 4808, 4809, 4810, 4811, 4812, 4841, 4842, 4843, 4844
- * (Chem): 4853, 4854, 4866, 4870, 4871, 4873, 4876, 4896, 4928, 4956, 4973, 4976, 4980, 4981, 4982, 4984
- * (Viral): 5031
- * (Immun): 5070, 5174, 5179
- * (Epid-Biom): 5291, 5296

5277 LIVER CANCER IN AFRICA. (Eng.) Linsell, C. A. (International Agency for Res. on Cancer, P.O. Box 46831, Nairobi, Kenya). *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 201-206.

Etiological factors in the high incidence of cancer of the liver in Africa are considered. Aflatoxins, produced by fungal contamination of stored cereals, are a possible factor, and several studies in Africa have established their presence in crops and food. Liver cancer incidence parallels exposure to aflatoxin contamination of food in Kenya and Swaziland. The sequelae, hepatitis - cirrhosis - cancer, is considered since viral hepatitis is endemic and occasionally epidemic in Africa. The viral hepatitis B antigen is associated with 60-66% of liver cancer in Kenya, Uganda and Mozambique. However, the antigens may not be causative factors, but may be merely 'passengers' in the unusual immunological state of the patient with liver cancer. The unusual epidemiological aspect of liver cancer in Africa is its appearance in young, previously healthy subjects. Eradication of liver cancer in Africa may come about as a result of the development of vaccines against hepatitis and improvement of crop storage to prevent aflatoxin production.

5278 CARCINOMA OF THE BLADDER IN THE RHODESIAN AFRICAN. (Eng.) Ritchie, J. W. K. (Royal Maternity Hosp., Belfast, Ireland); Weinberg, R. W. *J. R. Coll. Surg. Edinb.* 20(4):257-261; 1975.

A retrospective survey was made of 213 cases of carcinoma of the bladder that were handled in a Rhodesian, African teaching hospital in Salisbury. Carcinoma of the bladder is the third most common malignancy at this hospital and represents 25% of all the urological cases treated. The ratio of male to female was 3.2:1.0. The disease is commonest in the age group 40-60 yr. The most common complaint was pain: suprapubic in 144; in the loin or back in 43; and perineal in two patients. Frequency of urination, dysuria and hematuria were common urinary symptoms. Twenty three of 121 patients had been treated previously for *Schistoma haematobium* infestation. In 101 patients (52%) treatment was limited to sedation and analgesics alone. Some form of palliative treatment was given to 98 of the remaining 112 patients. The nine patients in whom a cytotoxic agent was administered were in poor condition. Bladder carcinoma is common in this community and the majority of patients present in late or terminal stages. The best results in terms of survival were obtained for 6.1% of the patients in whom the disease was diagnosed early. The authors suggest that use of cystoscopy for detection of schistosomiasis in patients presenting with hematuria may lead to early diagnosis of bladder carcinoma.

5279 A COMPARATIVE STUDY ON CANCER MORBIDITY OF THE FEMALE GENITALIA IN GEORGIAN, LATVIAN AND KAZAKH SSR. (Rus.) Charkviani, L. I.

(Res. Inst. Oncol. Georgian SSR Minist. Health, Tbilisi, USSR); Nugmanov, S. N.; Tabachnik, B. I.; Gvamichava, D. A. *Vopr. Onkol.* 21(3):74-81; 1975.

A comparative study of the incidence of carcinoma of the female genitals in Soviet Georgia, Latvia and Kazakhstan over a period of four years (1966-1970) was carried out. In all three republics, the cervix was most frequently affected (64.7%), followed by the ovaries (17.5%), uterine body (14.3%), vulva (2.3%) and vagina (1.7%). Kazakhstan had the highest (69.8%), Latvia the lowest incidence (49.1%) of cervical carcinoma. Of 100 malignancies of the female genitals, 15-16 women in Kazakhstan and Georgia, 25 in Latvia had ovarian carcinoma. In Latvia, the frequency of uterine body involvement (20.4%) was the highest. Carcinoma of the vulva was 3 times higher in Latvia, two times higher in Georgia than in Kazakhstan. In all three republics, an average of 43.4 women of 100,000 were afflicted each year between 1966-1970. It is of interest that no considerable difference as to incidence of carcinoma of the female genitalia between urban (45.65) and rural (40.89) population (per 100,000) was found. However, in Latvia the incidence is clearly higher among rural women. Out of 100,000 women in the three republics, 132 (30.45%) stricken with female cancer were 50-59 yr, 79.4 (10%) over 70 yr. It has been established that the incidence of carcinoma of the female organs has somewhat moved up to an older age group in 1970 compared to preceding years, obviously due to a generally higher life expectancy and institution of preventive measures against cancer.

5280 MAIN PRINCIPLES OF THE ORGANIZATION OF CANCER CONTROL IN USSR AND SELECTED DATA ON CANCER INCIDENCE. (Eng.) Trapeznikov, N. N. (Inst. Experimental and Clinical Oncology AMS, Moscow, U.S.S.R.); Strelkova, R. M.; Glebova, M. J. *Neoplasma* 22(4):449-458; 1975.

Oncological dispensaries, the basic unit for cancer treatment in the USSR, are described. In addition to providing prophylactic and therapeutic care for patients in their area, the units serve as cancer registries and educational centers. Statistical data on trends in the incidence of tumors in the USSR is presented. The over-all morbidity rate of neoplasms in the period 1965-1970 shows an upward trend for males and a slight downward slope for females. The trend in males reflects an increase in the incidence of malignant tumors of the trachea, bronchi and lungs. Males have a higher incidence of malignant tumors in all anatomical locations in almost all age groups. Incidence data from the republics of the USSR reveals regional differences in the anatomical locations of the most prevalent tumors. Peak incidence of neoplasms occurs under 50 years of age in females and over 50 in males. Mortality per 100,000 population is 165.8 for males and 91.6 for females and has remained stable for males but is decreasing for females. Higher male mortality is explained by the relative inaccessibility of their malignancies, i.e. in the stomach, lung, respiratory tract. In 1972, the five-year survival rate for all tumors was 46.2% and the ten-

year survival rate was 21.9%. Stomach neoplasms account for the highest mortality in both males and females, although the incidence rate of stomach neoplasms is down sharply from 1965. At present, there are 48,500 oncological beds representing 0.2/1000 population in oncological dispensaries and units attached to hospitals; future plans call for an additional 10,000 beds.

5281 PROSPECTIVE STUDIES ON CANCER EPIDEMIOLOGY BASED ON CENSUS POPULATION IN JAPAN.

(Eng.) Hirayama, T. (Natl. Cancer Center, Res. Inst., Tokyo, Japan). *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 26-35.

A population survey correlating cancer occurrence with selected risk factors was carried out in Japan over an eight year period. The study included 122,261 males and 142,857 females aged 40 years and above. Of the 21,167 deaths that occurred during this time, 5,560 were due to cancer. The highest standard mortality rates (SMR, rare or none = 1.00) were assessed for cigarette smoking, which enhanced cancer of all sites (SMR = 1.62). Initiation of smoking during the adolescent years and the number of cigarettes smoked appreciably increased the risk of cancer in the mouth (SMR = 7.04), larynx (SMR = 13.59), lung (SMR = 3.64) in males; and larynx (SMR = 6.52), lung (SMR = 2.03), and mediastinum (SMR = 7.54) in females. Daily intake of alcohol increased the risk of cancer at all sites (SMR = 1.07), especially the thyroid (SMR = 3.79). Milk consumption of 360 cc or more daily greatly lowered the risk of stomach cancer (SMR = .68). Nonsmokers who drank milk daily exhibited the lowest death rate from cancer at all sites (SMR = 0.48). Daily intake of meat, fish, and hot green-tea increased the risk of cancer of the mediastinum, urinary bladder, and mouth, respectively. Green-yellow vegetables reduced the risk of cancer in the esophagus (SMR = 0.57), mediastinum (SMR = 0.35) and prostate (SMR = 0.33). Finally, married women under the age of 30, showed an elevated SMR for cancer of the stomach of 2.24, and for the cervix 1.19. Women married after the age of 30 had a lowered SMR for cancer of the cervix (.50). Similarly, the risk of breast cancer in women with 1-2 children, 3-4 children, and 5 or more children had SMR with values of 1.37, 0.80, and 0.53, respectively.

5282 MULTIPLE STUDY APPROACHES (FOR CANCER) TO A WELL DEFINED POPULATION OF PARSIS.

(Eng.) Gangadharan, P. (Tata Memorial Hosp., Parel, Bombay, India); Jussawalla, D. J.; Rao, D. N.; Paymaster, J. C. *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 18-25.

A recent study on the relative frequency of the occurrence of cancer in the Parsi population, and

suggestions for expanding and interpreting these data are reported. The Parsis, residing near Bombay and representing 0.02% of the total population of India, are a religious sect who have maintained their ethnic and cultural identity. This study was performed over an eight year period on the entire Parsi population of 34,452 males and 35,612 females (1961 census figures). Almost 30% of the Parsi population was over 50 years old. The Parsis' socioeconomic condition is better than most other social groups and they are westernized in their food. Since very few Parsis smoke, oral and pharyngeal cancer are a minor problem. On the other hand, the number of cases of gastrointestinal cancer is relatively high. Cancer of the male breast, prostate, uterus, ovary, thyroid, and basal cell carcinomas were more frequent in Parsis than in others. The most remarkable variation in the comparison data is the high incidence rate of breast cancer among Parsi females. Breast cancer accounted for almost 49% of all cancer cases reported in females. The older age distribution of Parsis is thought to influence this relative frequency figure. Age adjusted studies indicate that the incidence rate of breast cancer among Parsis is still 1.7 times that of the total population of the Bombay area. Followup studies to stabilize data and isolate high risk factors are suggested through the use of standardized questionnaires. Laboratory analysis is also planned to carefully study the milk samples provided by lactating females.

5283 THE MATERIALS ON LEUKOSES STATISTICS IN SOCHI AND TUAPSE CITIES (1960-1971).

(Rus.) Lebedev, V. N. (Inst. Experimental Pathology and Therapy, U.S.S.R. Acad. Medical Sciences, Oncological Dispensary, Sochi, U.S.S.R.); Agaeva, E. M.; Belikova, S. G.; Savatenko, V. G. *Vopr. Onkol.* 21(8):50-54; 1975.

Statistical data on leukemia incidence, morbidity and mortality for Sochi and Tuapse during the 1960-1971 period are presented. A total of 428 cases were diagnosed, including acute leukemia in 115 patients (26.9%), chronic lymphatic leukemia in 110 patients (25.7%), chronic myeloid leukemia in 51 patients (11.9%), chronic reticulosis in 9 patients (2.1%), erythemia in 15 patients (3.5%), myelofibrosis in 11 patients (2.6%), lymphogranulomatosis in 46 patients (10.7%), reticulosarcoma in 54 patients (12.6%), and myeloma in 17 patients (4%). The mean annual morbidity per 100,000 inhabitants was 3.6 for acute leukemia, 3.46 for chronic lymphatic leukemia, 1.6 for chronic myeloid leukemia, 0.28 for chronic reticulosis, 0.49 for erythemia, 0.33 for myelofibrosis, 1.47 for lymphogranulomatosis, 1.65 for reticulosarcoma, and 0.53 for myeloma. The overall mean annual morbidity was 13.43 (14 in men, and 11.12 in women). The morbidity rate was highest in the age group over 60 yr with 50.16 (75.54 in men, and 35.88 in women). In the same age group, the acute leukemia morbidity was 5.96 among men, and 5.61 among women, while the chronic leukemia morbidity was significantly higher in men. The morbidity was lowest in the 10-29 yr age group with 2.56. The mean annual morbidity was 12.65 in the age group over 40 yr. The mortality was 72.6% (311 patients); including 35.5% from acute

leukemia, 35.8% from chronic leukemia, and 28.7% from destructively growing leukemias. The mean annual mortality per 100,000 inhabitants was 9.78; 1.92 in the 20-29 yr age group, and 40.09 in the age group above 60 yr. The leukemia incidence was 45.8/100,000 (32.4-56 in the different yr.) against 26.43 in certain other areas of the USSR. The incidence was 54.52 during the 1968-1969 period. The mean annual morbidity for malignant tumors was 244.44 during the 1967-1971 period, of which leukemias accounted for 14.62. During this period, leukemia caused the fifth highest morbidity among men (6.6%), and the 7th highest morbidity among women (5.5%). Leukemia caused the fourth highest mortality among men (8.5%), and the 6th highest mortality among women (9%).

5284 STOMACH AND COLON CANCER MORTALITY AMONG PUERTO RICANS IN NEW YORK CITY AND PUERTO RICO. (Eng.) Monk, M. (New York Medical Coll., Fifth Ave. at 106th St., New York, N.Y. 10029); Warshawer, M. E. *J. Chronic Dis.* 28(7/8):349-358; 1975.

Stomach cancer mortality rates for Puerto Rico migrants to New York City were lower than those for Puerto Ricans in Puerto Rico and higher than for other whites in New York City for the periods 1958-1962, 1963-1967 and 1968-1971. They were about midway between the rates for native-born whites in New York and those for nonmigrant Puerto Ricans. Colon cancer mortality rates for Puerto Rican migrants to New York were about the same as those in Puerto Rico in the 1960 period; in 1965, male rates for migrants rose nearly 90 per cent and remained at that rate in 1970. Female migrant rates rose slightly from 1960 to 1970, while in Puerto Rico rates for colon cancer for both sexes remained about the same. Colon cancer rates for other whites in New York were, in all three time periods, two to three times higher than those for Puerto Rican migrants. In contrast to studies on European or Oriental migrants the Puerto Rican data suggest that stomach cancer is more responsive to recent environmental exposure than colon cancer is. The recency of migration of Puerto Ricans and the small numbers of deaths from these cancer may limit the confidence placed in the conclusions from this study.

5285 AN EPIDEMIOLOGICAL STUDY OF LARYNGEAL CANCER IN JAPAN (1960-1969). (Eng.) Iwamoto, H. (Tokyo Women's Medical Coll., 10 Kawadacho, Shinjuku-ku, Tokyo, Japan). *Laryngoscope* 85(7):1162-1172; 1975.

An epidemiological study of laryngeal cancer was undertaken in Japan, based on 6,360 cases treated and registered during the period 1960 through 1969. The number of the patients increased 1.5 times from 1960 to 1969. Geographically the absolute number of recorded cases was proportional to the population density; i.e., it was larger in heavily urbanized areas and smaller in rural regions. An anatomical classification revealed that the incidence of supraglottic and glottic cancer was equal (3,121 and 3,176 cases), and subglottic

cancer was only 1% of the total. Histologically, 98.6% were squamous cell carcinoma, and 1.4% were basal cell carcinoma, adenocarcinoma, transitional cell carcinoma, anaplastic carcinoma, adenoid carcinoma, or lymphoepithelioma. The majority of the patients were 50-70 yr old, and those in their 60's were most numerous. The ratio between men and women was 9.6 to 1. 56.1% of the patients were found to have a blood relative with a history of cancer, and 31% were engaged in occupations where they used their voices frequently. Smoking habits were found in 96% of the patients surveyed, and as many as 52% were heavy smokers. Cigarette smoking might be regarded as a significant factor in laryngeal cancer, while alcohol consumption was not a significant factor.

5286 TOWARD THE PREVENTION OF LARYNGEAL CANCER. (Eng.) Wynder, E. L. (American Health Foundation, 1370 Ave. of the Americas, New York, N.Y. 10019). *Laryngoscope* 85(7):1190-1196; 1975.

Epidemiological data obtained from 1970-1973 on 258 male and 56 female patients with laryngeal cancer in various hospitals in large U.S. cities is presented. As in a previous study in 1956, cigarette smoking proved to be the highest risk factor in development of glottic and supraglottic cancers. High alcohol intake, particularly of hard liquor, enhances the effect of tobacco consumption, but in the absence of smoking does not increase the risk of laryngeal cancer. The cancer is more common in women today (male:female ratio is 4.6:1) than in 1956 (14.9:1) reflecting the fact that more women are now smokers. Smoking filter cigarettes for ten years or more reduces the risk of developing laryngeal cancer compared to smoking unfiltered cigarettes. Workers exposed to wood dust have a higher incidence of the cancer than those in other trades. Certain preventive measures are suggested: extending the anti-smoking campaign; smoking cessation clinics in every hospital; decreasing the tar yield of American cigarettes; prevention of alcoholism; protective measures for workers in high-risk occupations.

5287 EPIDEMIOLOGY OF LARYNGEAL CANCER. (Eng.) Krajina, Z. (Dept. Medical Faculty, Univ. Zagreb, Zagreb, Yugoslavia); Kulcar, Z.; Konić-Carnelutti, V. *Laryngoscope* 85(7):1155-1161; 1975.

Epidemiological data on 704 patients treated for cancer of the larynx at the Otolaryngology Clinic of Zagreb, Yugoslavia in the period 1945-1972 is presented. Patients were residents of Croatia, an area including the western and southern parts of Yugoslavia, with a Mediterranean and Continental climate. Only 3.8% of the cases in the study were females. The greatest number of cases, 593 or 82.2% were between 40-69 years of age; 38 were in their fourth decade and 66 in the eighth. Histologically, 664 were squamous cell carcinomas located almost exclusively in the supraglottic and glottic region of the larynx. Although the rural-urban population ratio in Croatia is 1:2, there were 424 cases from

rural areas and only 280 from urban. Smoking was heavily implicated in the etiology. Of the 677 men, 97.8% were smokers and the average patient had smoked 30 cigarettes a day for 30 years. Patients who were not smokers usually were either professional orators or chronically ill with laryngitis. Alcohol was probably not a factor in the development of the carcinoma, since 64% of the patients consumed little or none. The number of patients treated at the Zagreb Clinic doubled in the period 1959-1972 compared to the previous period, 1945-1959, although additional facilities for treatment became available in the latter period.

- 5288 RESIDUES IN FOOD AND FEED. PRELIMINARY SURVEY OF ETHYLENETHIOUREA RESIDUES IN THE CANADIAN FOOD SUPPLY, 1972. (Eng.) Pecka, Z. (Quebec Regional Lab., Health Protection Branch, Dept. Natl. Health and Welfare, 1001 St-Laurent, Longueuil, Quebec, Canada); Baulu, P.; Newsome, H. *Pestic. Monit. J.* 8(4):232-234; 1975.

A preliminary monitoring program was initiated to determine ethylenethiourea (ETU) content of the Canadian food supply. Of 167 samples analyzed, 90 were domestic and 77 were imported. Samples were analyzed by electron-capture/gas-liquid chromatography. Thirty-three percent of the samples contained detectable ETU residues; most of these were 0.020 ppm or less. Highest levels, 0.047 and 0.083 ppm, were found in canned spinach and orange peel, respectively.

- 5289 DETERMINATION OF PROPORTION OF DIVIDING CELLS IN THE LEUKEMIC POPULATION IN ACUTE LEUKEMIA. (Rus.) Vladimirskaia, E. B. (Clin.-Hematol. Lab., Inst. Pediatr. Acad. Med. Sci. USSR, Moscow, USSR). *Problemy Hematologii i Perelivaniya Krovi* 20(3):8-13; 1975.

A method for the determination of the percentage of dividing cells in the leukemic population in acute leukemia is described, and general pathogenetic and therapeutic implications of the findings are discussed. The quantitative determination of the dividing subpopulation is based upon the comparison of *in vitro* autoradiographic data obtained by incubation with tritiated thymidine for 1 hr with karyometric data for the entire leukemic cell population. Results obtained for ten children with acute leukemia, one child with autoimmune hemolytic anemia, and another child with chronic unspecific lymphadenitis show that the percentage of dividing cells in acute leukemia is lowest in the initial phase (one case), in a period preceding remission (two cases), and during clinical remission (one case). This population was highest in one patient with a tumorous form of acute leukemia (70.6%), and in the prefinal stages of the process in two patients with 55% and 55.5%, respectively. The percentage of dividing cells was 15% in hemolytic anemia, and 45.7% in chronic unspecific lymphadenitis, which may be related to the leukemic process. The findings indicate a relationship between the ratio of dividing to non-dividing subpopulations and the source of the leukemia. The non-dividing leukemic

subpopulation is a potential source of cells for the dividing subpopulation, and the increase in the percentage ratio of the latter leads to a disruption of the remission and recurrence at a given moment.

- 5290 THE ACCEPTANCE OF RISK. (Eng.) Pochin, E. E. (Natl. Radiological Protection Board, Harwell, U.K.). *Br. Med. Bull.* 31(3):184-190; 1975.

- 5291 MULTIPLE SEQUENTIAL SKIN CANCERS: THE RISK OF SKIN CANCER IN PATIENTS WITH PREVIOUS SKIN CANCER. (Eng.) Bergstresser, P. R. (Miami Veterans Administration Hosp., 1201 NW 16th St., Miami, Fla. 33125); Halprin, K. M. *Arch. Dermatol.* 111(8):995-996; 1975.

- 5292 RISK OF SECOND TUMORS IN SURVIVORS OF CHILDHOOD CANCER. (Eng.) Li, F. P. (Natl. Cancer Inst. Field Station, 35 Binney Street, Boston, Mass. 02115); Cassady, J. R.; Jaffe, N. *Cancer* 35(4):1230-1235; 1975.

- 5293 MORTALITY FROM CANCER OF THE UTERINE CERVIX IN DENMARK 1961-1971. (Dan.) Grünfeld, K. (Danish Inst. Clin. Epidemiol., Copenhagen, Denmark); Horwitz, O.; Lysgaard-Hansen, B. *Ugeskr. Laeger* 137(5):251-259; 1975.

- 5294 ANGIOSARCOMA OF THE LIVER AS THE CERTIFIED CAUSE OF DEATH 1963-1973. (Eng.) Baxter, P. J. (Employment Medical Advisory Service, Health and Safety Executive, Baynards House, 1 Chepstow Place, London W2 4TF, England); Fox, A. J. *Lancet* 2(7923):27-28; 1975.

- 5295 GASTRO-INTESTINAL MALIGNANCIES IN LUDHIANA. (Eng.) Sabharwal, B. D. (Dayanand Medical Coll., Ludhiana, India); Prabhakar, H.; Prabhakar, B. R. *J. Indian Med. Assoc.* 64(3):57-60; 1975.

- 5296 STUDY OF THE DISTRIBUTION OF HAPTOGLOBIN GROUPS IN MARSEILLE IN NORMAL SUBJECTS AND IN TUMOR PATIENTS. (Fre.) Kleisbauer, J. P. (Institut d'Etudes et Recherches pneumophthysiologiques, Hopital Sainte-Marguerite, 13009 Marseille, France); Poirier, R.; Artinian, H.; Arnoux, A.; Laval, P. *C. R. Soc. Biol. (Paris)* 169(3/Suppl.):811-814; 1975.

- 5297 THE CHANGING PATTERN OF NEOPLASTIC DISEASE IN CANADIAN ESKIMOS. (Eng.) Schaefer, O. (Northern Medical Res. Unit, Charles Camell Hosp., 12815-115 Ave., Edmonton, Alta. T5M 3A4, Canada); Hildes, J. A.; Medd, L. M.; Cameron, D. G. *Can. Med. Assoc. J.* 112(12):1399-1404; 1975.

5298 SOME OBSERVATIONS ON THE ETIOLOGY OF ORAL CANCER. (Eng.) Khanna, N. N. (Inst. of Medical Sciences, Banaras Hindu Univ., Varanasi-221005, India); Pant, G. C.; Tripathi, F. M.; Sanyal, B.; Gupta, S. *Indian J. Cancer* 12(1):77-83; 1975.

5299 THE ENVIRONMENT AND NASOPHARYNGEAL CANCER. (Eng.) Muir, C. S. (International Agency Res. Cancer, Lyon, France); Day, N. E. *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 314-318.

5300 DETECTION OF 3,4-BENZOPYRENE IN THE WATER AND ORGANIC SEDIMENTS OF BRACKISH SEA WATER OF THE POLYNESIAN ATOLLS. STUDY OF CERTAIN BIOTIC AND ABIOTIC FACTORS INVOLVED. (Fre.) Niasusat, P. M. (Division de Biologie Generale et Ecologie, Centre de Recherches du Service de Sante des Armees, France); Trichet, J.; Heros, M.; N'Guyen Trung Luong; Ehrhardt, J. P. *C. R. Acad. Sci. [D] (Paris)* 281(14):1031-1034; 1975.

5301 VARIATION OF CELL KINETIC PARAMETERS IN RELATION TO THE GROWTH RATE OF THE EHR- LICH ASCITES TUMOR. (Eng.) Woo, K. B. (Div. of Cancer Treatment, Natl. Cancer Inst., Bldg. 37, Rm. 1B23, Bethesda, Md. 20014); Wiig, K. M.; Brenkus, L. M. *Cell Tissue Kinet.* 8(4):387-390; 1975.

See also:

- * (Rev): 4802, 4803, 4805, 4806, 4813, 4823, 4824, 4825, 4827, 4831, 4844, 4845, 4846, 4847, 4848, 4849
- * (Chem): 4870, 4873, 4888, 4931, 4976
- * (Viral): 5013, 5018
- * (Immun): 5069, 5104, 5106
- * (Path): 5207, 5271, 5275

- 5302 GROUP CLASSIFICATION OF BIOLOGICAL TISSUES BY INFRARED SPECTROSCOPY. (Eng.) Deb, K. K. (Nat'l. Cancer Inst. Frederick Cancer Res. Cent., Md.). *Spectrosc. Lett.* 8(4):185-200; 1975.

The feasibility of using the frustrated multiple internal reflection technique to obtain IR spectra of sufficiently high quality to permit the characterization of biologically important tissue components was investigated. Thirteen wet, freshly removed specimens (fat, external skin, tail tendon skin, lung, kidney, heart, abdominal muscle, thymus, spleen, brain, liver, blood serum from the heart and from the kidney) from a rat were examined as were an RNA tumor virus (Rauscher type), and RNA and DNA samples. In all the spectra shown, the gross spectral features in the protein polyamide region ($3400-1300\text{ cm}^{-1}$) resemble one another although they display characteristic changes in the region below 1300 cm^{-1} . The region of skeletal vibrations appeared to be most informative for tissue discrimination. Since the materials under investigation are so complex, each absorption in this region reflects the probability of several composite structures. Structural interpretation based on observed IR frequency would, therefore, be mainly qualitative. It is concluded that all the tissues examined can be grouped into four different categories on the basis of their IR spectra. The most important differences are in the shape and relative depths of characteristic absorptions appearing in the region of skeletal vibration. Spectra of rat fat, external skin, tail tendon skin, lung, heart and abdominal muscle tissue are alike (Group 1). Rat thymus and spleen (Group 2) have identical spectra except for the bands 1300 and 1180 cm^{-1} , which are most distinct in the spectrum of thymus. The spectra of rat brain (Group 3) is characterized by a broad band at 1060 cm^{-1} . The gross structure of the spectrum closely resembles those of RNA and DNA. The spectrum of normal rat liver (Group 4) has a broad adsorption centered at 1040 cm^{-1} . The spectrum of dimethylnitrosamine-injected rat liver (3 mg/450 g rat) sacrificed 24 hr after injection shows that the carcinogenic influence appreciably reduced the concentration of liver glycogen to such a low value that the glycogen band almost disappeared from the spectrum. It is suggested that the frustrated multiple internal reflection technique may be useful for the rapid detection of induced changes in tissue composition.

- 5303 ISOLATION AND SUBFRACTIONATION ON FICOLL GRADIENTS OF ADULT RAT HEPATOCYTES: SIZE, MORPHOLOGY, AND BIOCHEMICAL CHARACTERISTICS OF CELL FRACTIONS. (Eng.) Drochmans, P. (Laboratoire de Cytologie et de Cancerologie Experimentale, Universite Libre de Bruxelles, 100 Bruxelles, Belgium); Wanson, J. C.; Mosselmans, R. *J. Cell Biol.* 66(11):1-22; 1975.

A method is described for isolating hepatocytes from the livers of adult rats. The livers are subjected to recirculating perfusion with a Ca^{++} -free Hanks' solution, which releases the adhesiveness of the cells and cleaves the desmosomes. The addition of collagenase and hyaluronidase to the perfusion medium causes a complete dissociation of

the liver tissue into a mixture of isolated cells and cell cords in which the hepatocytes remain connected with specific junctional differentiations, i.e., gap and tight junctions. The individual cells are released by gentle rolling of the suspension of cell trabeculae; the gap junctions are ruptured in at least one of every two adjacent cells, generally remaining attached with a small portion of cytoplasm to the other cell. With this technique, 60-65% of the parenchymal cells within a Sprague-Dawley rat liver could be isolated, and endothelial cells and other connective tissue cells were not recovered. The ultrastructure of the isolated hepatocytes was well preserved and the glucose-6-phosphatase activity of most cells was unaltered. Protein, DNA, and RNA recovery in the hepatocyte preparations was satisfactory, amounting to 70% of that found in liver homogenates. However, glycogen was partially lost or degraded during the manipulations. Measurement of cell diameters confirmed the preservations of the original volume of *in situ* hepatocytes and indicated the presence of more than one type of parenchymal cells. Analysis of the heterogeneous population by isopycnic density gradient centrifugation demonstrated the presence of two types of hepatocytes: light hepatocytes, with a mean diameter of $20.5\text{ }\mu\text{m}$ and a mean density of 1.10, were characterized by an extended smooth endoplasmic reticulum entrapping dispersed α -glycogen particles; and heavy hepatocytes, with a mean diameter of $19.0\text{ }\mu\text{m}$ and a mean density of 1.14, presented a relatively reduced compartment of smooth endoplasmic reticulum but large accumulations of glycogen. It is suggested that the low density cell fraction is enriched in centrilobular cells, and the high density fraction is enriched in perilobular hepatocytes.

- 5304 CHARACTERIZATION OF A RAT LUNG MICROSOMAL FRACTION OBTAINED BY SEPHAROSE 2B ULTRAFILTRATION. (Eng.) Capdevila, J. (Dept. Forensic Medicine, Karolinska Institutet, S-104 01 Stockholm 60, Sweden); Jakobsson*, S. W.; Jernstrom, B.; Hellia, O.; Orrenius, S. *Cancer Res.* 35(10):2820-2829; 1975.

A new procedure for obtaining rat lung microsomes essentially free of interfering hemoproteins is described. The method includes Sepharose 2B column chromatography of the $12,000 \times g$ supernatant of lung homogenates, followed by ultracentrifugation of the material eluted in the void volume. Microsomes isolated in this manner contain specific levels of cytochromes b_5 and P-450 and of NADPH-cytochrome c reductase that were among the highest ever reported for a rat lung microsomal fraction. After treatment of male Sprague-Dawley rats with 3-methylcholanthrene (20 mg/kg daily for three days, ip) the specific content of cytochrome P-450 in lung microsomes was doubled, and that of cytochrome b_5 increased 1.5 times. Several spectral differences between hepatic and lung microsomal cytochrome P-450 were apparent. In lung microsomes, the maximum of the reduced CO-bound cytochrome complex in a different spectrum was at 453 nm for the noninduced hemoprotein and shifted to 451 nm after 3-methylcholanthrene induction. In contrast, no signifi-

cant change in the ethylisocyanide difference spectra of reduced microsomes was obtained after induction; moreover, the spectra obtained with induced and non-induced cytochrome P-450 were similar to the one shown by hepatic microsomes from polycyclic hydrocarbon-treated rats. Furthermore, spectrophotometric studies on *n*-octylamine binding to control and induced lung cytochrome P-450 yielded results different from those previously obtained with rabbit liver microsomes. It is concluded that the cytochrome P-450 present in rat lung microsomes before and after 3-methylcholanthrene treatment is distinctly different from the liver hemoprotein.

5305 MOUSE EPIDERMAL CELL CULTURES: II. ISOLATION, CHARACTERIZATION AND CULTIVATION OF EPIDERMAL CELLS FROM PERINATAL MOUSE SKIN. (Eng.) Fusenig, N. E. (German Cancer Res. Center, Inst. for Biochemistry, 69 Heidelberg 1, Im Neuenheimer Feld 280, West Germany); Worst, P. K. M. *Exp. Cell Res.* 93(2):443-457; 1975.

In order to initiate studies on chemical carcinogenesis in an *in vitro* system analogous to mouse epidermis, primary epidermal cell cultures from perinatal C3H mouse skin were established. A standardized method for the large-scale isolation of epidermal cells from late embryonic or newborn mouse dorsal skin was developed. The epidermal cells were separated from fibroblasts by two series of discontinuous Ficoll density gradients. Using 80 - 100 animals per experiment, an average yield of 3×10^6 viable epidermal cells per animal was obtained. The viability of the purified cell suspension exceeded 95%, and the plating efficiency, representing the growing cell fraction 24 hr after plating, was about 43%. The cultures started as epithelial monolayers without fibroblast contamination. Their epidermal nature and origin was proved immunologically by an *in vivo* absorbed rabbit anti-mouse epidermis antiserum. The purity of the epidermal cells was quantitatively determined in trypsinized suspensions by the indirect immunofluorescence test yielding more than 95% epidermal antigen-positive cells. About half of the remaining antigen-negative cells could be identified as melanocytes. These highly purified epidermal cells grew *in vitro* for 2-3 wk without dermal constituents or diffusible mesenchymal factors. The monolayers differentiated in culture giving rise to keratinizing cell sheets on top of the proliferating basal layer. By morphological, histochemical and physical methods, the differentiation processes *in vitro* were observed to be quite similar to keratinization *in vivo*. The methods for isolation and cultivation of perinatal mouse epidermal cells reported here are advantageous because they can be well standardized with regard to cell yield, viability and purity, as well as reproducibility.

5306 STUDIES OF TUMOR CELL LINES DERIVED FROM PATIENTS WITH MALIGNANT MELANOMA. (Eng.) Gerner, R. E. (Dept. Surgery, Roswell Park Memorial Inst., N.Y. State Dept. Health, Buffalo, N.Y.); Kitamura, H.; Moore, G. E. *Oncology* 31(1):31-43; 1975.

The establishment and characterization of 14 long-term human malignant melanoma cell lines from biopsy specimens, malignant effusions, and the peripheral blood are described. Cells and clumps of cells were removed from the biopsy specimen and placed in an incubator-shaker to free a greater number of the tumor cells. The suspension of cells was aspirated into a culture flask ($0.5-2 \times 10^6/\text{mm}$ culture fluid). Varieties of culture media were used but in all instances the media was supplemented with 20% fetal calf serum and the pH was adjusted to 7.2. Definite growth of tumor cells took place in no more than 30% of the cultures and in only 15% could the cell growth be continued for more than three months. The fluid from effusions was collected in bottles to which 50-150 mg heparin/2000 ml volume had been added. The bottles were centrifuged and the cell pellets resuspended in culture media as for the solid tumor cells. Cells were removed from each cell line for analysis of the chromosome constitution, morphological characteristics, determination of doubling times, and studies of the ultrastructure of the cells. The tumorigenicity of the melanoma cell lines was tested by inoculating immunosuppressed newborn mice with 0.1 ml of $0.5-2.0 \times 10^6$ tumor cells. Localization of melanin synthesis was attempted by growing several cell lines with and without tyrosine; aliquots of each cell line were then examined by electron microscopy. Of the 14 cell lines, three have been maintained in continuous monolayer culture for over six years. The morphological features of these cell lines have remained constant during *in vitro* maintenance with the exception of a partial loss of melanin production. Two of the cell lines have continued synthesis of pigment in culture for more than six years. The chromosome constitution of the 14 cell lines has remained relatively constant; all of the lines have abnormal chromosome constitutions covering a spectrum of 40 to several hundred chromosomes/cell. In most cell lines, there are one or more marker chromosomes. As few as 100,000 cultured cells produced tumor masses in immunosuppressed newborn mice. Premelanosomes, melanosomes, and/or melanin granules were seen in all cell lines under the electron microscope. The melanin granules were scattered throughout the cytoplasm and even in the microvilli. Some of the theoretical uses of human melanoma cell lines are summarized and the need for caution in handling these human malignant cells is emphasized.

5307 KINETIC CHARACTERISTICS OF THE DEVELOPMENT OF A NEW LEUKEMIA LINE IN MICE. (Rus.) Nikol'skaia, T. A. (Inst. Phys. Chem., Acad. Sci. U.S.S.R., Moscow, U.S.S.R.); Erokhin, V. N.; Emanuel, N. M. *Dokl. Akad. Nauk SSSR* 221(4): 967-969; 1975.

The kinetic characteristics of the new mouse lymphatic leukemia line CL, induced in C57Bl/6 line adult mice by ip transplantation of a cell-free extract of leukemic lymphoblast culture, were established by measuring the weight of mesenteric and inguinal lymph nodes, or the liver, and the total leukocyte count in the peripheral blood as a function of time during the first 12 days of the tumorous process. Sinusoidal kinetic curves were obtained for the increases

in the lymph node and liver weights and in the leukocyte count. The curves can be described by kinetic equations of first-order autocatalytic reactions. The well-established kinetic characteristics of the lymphatic leukemia line CL suggest the use of this line in the control of the efficiency of antineoplastic drugs.

- 5308 GROWTH AND COMPOSITION OF A TRANSPLANTABLE MURINE LEYDIG CELL TUMOR. (Eng.) Neaves, W. B. (Univ. Texas Health Science Center, 5323 Harry Hines Blvd., Dallas, Tex. 75235). *J. Natl. Cancer Inst.* 55(3):623-631; 1975.

A transplantable murine testicular tumor, M5480, served as a model of Leydig cell function; the parameters investigated included tumor growth rates, the proportion of nucleated cells composing the tumor at different ages, changes in the ratio of healthy and degenerate cells, a classification of cell types, and ultrastructural characteristics of the cells. C57BL/6J mice were inoculated sc with 50 mg of M5480. The animals demonstrated a reproducible pattern of slow tumor growth up to day 10 followed by rapid growth at the rate of approximately 0.5 g per day through day 27. The mean survival time of tumor-bearing mice was 33 days, when tumor weight accounted for more than 25% of total body weight. The rapid increase in weight occurring around day 10 resulted largely from a 20-fold increase in the quantity of extravasated blood inside the tumor, which in turn promoted a 50% reduction in host hematocrit. Sustained enlargement of M5480 during the third and fourth weeks of growth was supported by proliferation of tumor cells. Apart from blood-filled cavities, over 90% of the tumor consisted of neoplastic Leydig cells exhibiting generalized cytoplasmic features usually associated with mitotic activity. An activity macrophage was the next most abundant cell type, accounting for 2-3% of the nucleated cell mass. The remaining 3% was occupied by vascular elements, WBC, and giant cells. Depending on the age of the tumor, varying proportions of the cell population showed signs of anoxic degeneration. Degenerate cells were minimal at day 14, accounting for less than 4% of the total population, and maximal beyond day 21, when they occupied more than 50% of the cell mass. This suggests that 14-day-old malignancies may be the optimum source of Leydig cells for *in vitro* studies of gonadotropin-stimulated steroidogenesis.

- 5309 HUMAN NEUROBLASTOMAS *IN VITRO*: ACTIVATION OF THE MEMBRANE PUMP FOR CATECHOLAMINES BY 5-BROMODEOXYURIDINE. (Eng.) Goldstein, M. N. (Dept. Anatomy, Washington Univ., St. Louis, Mo.); Brodeur, G. M. *Proc. Int. Cancer Congr.* 11th. Vol. 1. (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 178-182.

The effects of 5-bromodeoxyuridine (BUDR) and nerve growth factor (NGF) on the expression of the catecholamine pump in two recently established lines of

human neuroblastoma (NMB and NGP) were studied. The trypsinized cells were grown in medium containing 200 ng/ml of 2.5 S mouse NGF and/or 3×10^{-7} or 5×10^{-6} M BUDR. After 8-10 days, the cells were pulse labeled with [3 H]-dopamine (10 μ Ci/ml), fixed in 3% glutaraldehyde, and studied by autoradiography. For scintillation counting, the cultures were pulse labeled with 0.5 μ Ci/ml of [3 H]-dopamine. In some experiments, neuroblastoma cells grown in the presence of NGF, BUDR, and/or thymidine for 8-12 days were exposed to fluorescent light for 1-3 hr; the cultures were observed for 7 days thereafter. Line NMB contained small epithelium-like cells with short neurites, neuroblasts, spindle-shaped cells, and clusters of larger epithelial cells, while line NGP contained a very uniform population of small, stubby-shaped cells, most without neurites. NGF produced a rapid outgrowth of neurites from NGP cells, while only the epithelial cells of the NMB line showed slow neurite outgrowth. Lysed cells from both lines grown in BUDR (10^{-6} M or higher) were transformed into giant cells. In lower concentrations of BUDR, there was a gradual flattening of the cells and a more extensive outgrowth of neurites. The large epithelioid cells of line NMB were induced to develop neurites in BUDR medium. NGF prevented the toxic effects of BUDR on some NGP cells and amplified the BUDR-stimulated outgrowth of neurites. Ganglion cells were more common in cells grown in BUDR plus NGF than in untreated cells or cells grown in NGF alone. Tumor cells grown in BUDR or BUDR plus NGF were intoxicated by fluorescent light. Cells grown in BUDR concentrated dopamine, while control cells and cells grown in NGF did not. The uptake of label increased as the cells increased in size and their neurites became longer. The mechanism of action of BUDR is not known.

- 5310 HIGH EXTRACELLULAR FIBRINOLYTIC ACTIVITY OF TUMORS AND CONTROL NORMAL TISSUES. (Eng.) Chibber, B. A. (Purdue Univ., West Lafayette, Indiana); Niles, R. M.; Prehn, L.; Sorof, S. *Biochem. Biophys. Res. Commun.* 65(2):806-812; 1975.

To determine whether or not high extracellular proteolytic activity is a general tumor phenotype, the levels of extracellular fibrinolytic activity due to plasminogen activation in the primary cultures of ten lines of immunogenic and nonimmunogenic transplanted sarcomas of mice were examined. The levels of activity were compared with those of their normal control tissues, muscle and skin. Five lines were originally induced by sc pellets of methylcholanthrene in C3H mice, and the other (nonimmunogenic) sarcomas were derived by spontaneous transformation of C3H x C57BL mouse embryo cultures. They were serially passaged sc 3-19 times in male C3H x C57BL mice that had been thymectomized 1-3 wk prior to passage and had been X-irradiated (550 R). Both the normal control muscle and skin, as well as all tumors had high and moderate levels of extracellular fibrinolytic activity. The data therefore do not support the hypothesis that high extracellular proteolytic (fibrinolytic) activity is either a general tumor phenotype, or a property which may offer signifi-

cant advantage over normal cells for positive selection in tumor growth and invasiveness.

- 5311 GROWTH ENHANCEMENT OF MYOGENIC TUMOR CELLS BY CONDITIONED MEDIUM FROM EMBRYO FIBROBLASTS. (Eng.) Baker, R. S. U. (Sch. Public Health and Tropical Medicine, Univ. Sydney, N.S.W. 2006, Australia); Aw, E. J. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):321-326; 1975.

The ability of conditioned medium from mouse embryo cultures to enhance colony formation in myogenic and nonmyogenic murine cells was investigated. Growth medium was conditioned by 72-hr incubation on the mouse embryo cells *in vitro*. Supplementation of agar suspension cultures with conditioned medium from primary cells, but not from established lines, readily enhanced colony development by mouse tumor cells including murine sarcoma virus-induced thigh tumors from Prince Henry of BALB/c mice. Only cells with the properties of myoblasts responded to conditioned medium. Other fibroblastoid cells and virus-transformed cell lines were not affected. Myogenic cells in agar cultures not differentiate. Soluble collagen at 400 µg/ml comparison with fresh conditioned medium. It is concluded that myogenic tumor cells in agar suspension offer a useful system for investigating factors that enhance survival and replication of muscle cells.

- 5312 CONTROL BY CELL INTERACTION OF PHOSPHATE UPTAKE IN 3T3 CELLS. (Eng.) Harel, L. (Institut de Recherches Scientifiques sur le Cancer, 94800 Villejuif, France); Jullien, M.; Blat, C. *Exp. Cell Res.* 90(1):201-210; 1975.

The hypothesis that an increase in cell concentration will decrease phosphate metabolism was investigated. 3T3 cells grown to stationary phase in monolayers and then trypsinized and incubated in suspension, displayed an increase in phosphate uptake when the cell concentration was decreased from 10^6 cells/ml to 10^5 cells/ml. Where the cell concentration was further reduced from 10^5 cells/ml to 2.5×10^4 cells/ml there was no further increase in the rate of phosphate uptake. On the contrary, a small decrease was observed. The "concentration effect" (the decrease of phosphate uptake when the cell concentration increases from 10^5 to 10^6 cells/ml) was larger when cells originated from a culture in stationary phase than when they originated from a culture in log phase. The "concentration effect" could be observed ten minutes after cell incubation, but was larger after a lag time of 40 min incubation. Differences in the "concentration effect" could be noted between 3T3 and SV3T3 cells. In SV3T3 cells, no significant variations of phosphate uptake were observed when the cell concentration was changed. Thus, differences between phosphate uptake in 3T3 and SV3T3 cells are large when cells are incubated at high concentrations or at high densities, and small when they are incubated at low concentrations or at low densities. The "concentration effect" in 3T3 cells supports the assumption that inter-

actions between cells cause the decrease of phosphate metabolism in dense culture. Diffusion of an inhibitor into the medium may explain the data.

- 5313 THE RESPONSE OF CULTURED HUMAN NORMAL GLIAL CELLS TO GROWTH FACTORS. (Eng.) Westermarck, B. (The Wallenberg Lab., Uppsala Univ., Uppsala, Sweden); Wasteson, A. *Adv. Metab. Disord.* 8:85-100; 1975.

A glial cell assay was used for determining growth factors, and these growth properties are described. In addition, different substances were analyzed for their growth promoting activities. Explanted human adult brain tissue was fragmented and plated in Eagle's minimal essential medium containing 10% calf serum and antibiotics. Cultures were transferred after 14 days and experiments were performed on cells in the proliferation phase. Withdrawing serum from the exponentially growing glial cells resulted in a rapid decrease in the fraction of cycling cells visualized by a decreased labeling index after pulse labeling with [3 H]thymidine. Quantitative measurements of the DNA content of single cells showed that the cells were blocked in the G₁ phase. An increased fraction of cells in DNA synthesis was noted 12-16 hr after the addition of growth promoting substances to cultures deprived of serum for 24-48 hr. The potency and concentration of the growth promoters determined the magnitude and duration of the proliferation wave; the time period in which DNA synthesis was initiated was not influenced by these factors. Somatomedin, a polypeptide fraction isolated from human plasma, was a potent glial stimulator; its effect was detectable at doses as low as 2.5 µg/ml. This polypeptide was 50 times as effective per microgram dry weight as calf serum. Fibroblast growth factor, a polypeptide isolated from bovine pituitary gland, given at 2-fold dilutions from 1 µg/ml to 7.8 ng/ml, was a potent growth factor; the optimal effect was observed at 31.25 ng/ml. Growth factors released in the culture media of six neoplastic and two normal human cell lines were also analyzed for growth promoting ability. The cell lines used were: one osteosarcoma line (2 OS), one synovial sarcoma line, four glioma lines, one glial line, and one line of human embryonic lung fibroblasts. The culture medium of the 2 OS cultures contained significant activity and was 40 times as active as calf serum per microgram protein. It was demonstrated that human serum prepared from whole blood had better growth-promoting activity than serum prepared from cell-free plasma, indicating that the major part of growth promoting activity was generated by interacting platelet and plasma factors. This finding is consistent with the concept that the growth factor, *in vivo*, exists as an inactive precursor that can be activated when platelets release their contents.

- 5314 SPONTANEOUS MATURATION AND DIFFERENTIATION OF B16 MELANOMA CELLS IN CULTURE. (Eng.) Kreider, J. W. (Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa.

17033); Schmoyer, M. E. *J. Natl. Cancer Inst.* 55(3):641-647; 1975.

B16 melanoma tumors and cultures are composed of cells with different melanin contents and replicative activities. The hypothesis was tested *in vitro* that these various cells constituted a population in the process of differentiation and maturation. Early cultures were predominantly composed of small, amelanotic cells with high replicative activity. Older cultures contained mostly larger and heavily melanotic cells with little or no replicative activity. Replicative activity, as measured by the uptake of tritiated thymidine, was inversely proportional to cell size and melanin content. Colony-forming ability was impaired if the original cells were melanotic. Tumorigenicity was unaffected except in very old (9-day) cultures. The results support the concept that malignant melanocytes undergo a sequence of developmental changes which eventuates in the production of mature cells characterized by enlargement, elevated melanin content, and reduced replicative and colony-forming capacity.

5315 RELATIONSHIP OF THE BIOSYNTHESIS OF α -FETOPROTEIN, ALBUMIN, HEMOPEXIN, AND HAPTOGLOBIN TO THE GROWTH STATE OF FETAL RAT HEPATOCYTE CULTURES. (Eng.) Sell, S. (Univ. California, San Diego, Medical Sch., La Jolla, Calif. 92037); Skelly, H.; Leffert, H. L.; Muller-Eberhard, U.; Kida, S. *Ann. N.Y. Acad. Sci.* 259:45-48; 1975.

Use of a fetal rat hepatocyte culture system to delineate the relationship between cell proliferation and the synthesis and release of α -fetoprotein (AFP) and albumin obviated technical difficulties and problems of interpretation of *in vivo* experiments. Long-term primary cultures were derived from collagenase-treated rat liver tissue, suspended in arginine-free plating medium containing ornithine and fetal bovine serum, and placed in Falcon plastic culture dishes. Proliferation of hepatocytes occurred from days 2-8 to produce arginine-synthesizing quiescent monolayers. The quiescent layers could be stimulated to further proliferation by addition of fresh serum containing arginine. The proteins in the culture medium and in cell lysates were measured by radioimmunoassays for AFP and albumin based on radioactive leucine uptake and immune precipitation procedures. Assays for haptoglobin and hemopexin were also carried out in one set of experiments. Cell proliferation was determined by cell counts and DNA synthesis by uptake of ^3H -thymidine. AFP and albumin were produced by arginine-synthesizing fetal rat hepatocytes *in vitro*. AFP and hemopexin production were coupled to hepatocellular proliferation, whereas albumin and haptoglobin production were not. During the cell cycle, AFP was synthesized prior to phase S and released prior to phase M. It is proposed that AFP may play a role in the regulation of hepatocellular growth through estradiol binding and modulation of the intracellular concentration of very low density lipoprotein.

5316 EFFECTS OF BIOTIN DEPLETION ON MOUSE LEUKEMIC CELLS IN CULTURE. (Eng.) Pienkowska, K. (Inst. for Drug Res. and Control, 00-725 Warsaw, Chelmska 30-34, Poland); Koziorowska, J. *Biochem. Biophys. Res. Commun.* 66(3):1024-1029; 1975.

The effects of biotin deficiency on the growth, the content of L-aspartate, and on chromosomal aberrations of L5178Y murine leukemic cells are reported. Cells grown for three passages in Fischer's medium including biotin were found to contain 0.27 ng of biotin/mg of protein. When grown in the same medium lacking biotin, the cell content of biotin was reduced to 0.12 ng/mg, and this fell to undetectable levels when avidin (0.02 $\mu\text{g}/\text{ml}$) was also included in the medium. The average numbers of cells accumulating after 96 hr of incubation was correspondingly reduced from about $10^6/\text{ml}$ after growth in the complete medium to $5 \times 10^5/\text{ml}$ in the biotin-deficient medium and $3.5 \times 10^5/\text{ml}$ in the biotin-deficient plus avidin medium. The cellular content of L-aspartate also diminished from a level of 64 $\mu\text{g}/\text{mg}$ protein in cells grown in the complete medium, to 43 $\mu\text{g}/\text{mg}$ in those cells grown in the avidin-containing medium. Growth in the avidin-containing medium also resulted in an increase from 1% to 24% in the proportion of colchicine-arrested metaphases that were morphologically abnormal. It is concluded that the L5178Y cells are, unlike HeLa cells, unable to acquire the ability to synthesize biotin in conditions of deficiency, and that the resulting depletion of biotin results in an impairment of L-aspartate synthesis. This impairment may explain, at least partly, the increase in chromosomal disturbances observed in cells deficient in biotin, because of the involvement of this amino acid in the synthesis of purines and pyrimidines.

5317 GROWTH-ENHANCING PROTEIN OBTAINED FROM CELL SURFACE OF CULTURED FIBROBLASTS. (Eng.) Igarashi, Y. (Natl. Cancer Cent. Res. Inst., Tokyo, Japan); Yaoi, Y. *Nature* 254(5497):248-250; 1975.

Chick embryo exudates were used to detect proteins thought to have a growth enhancing factor obtained from the surface of cultured fibroblasts. Monolayer cultures were prepared in Eagle's MEM supplemented with bovine serum. Cells were then washed with EDTA and incubated with Tris buffer containing urea and EDTA. Maximum growth enhancement of protein fractions was obtained by 40 $\mu\text{g}/\text{ml}$ of the crude extract but higher concentrations caused an inhibitory factor to the proliferating cell. Treatment of the concentrated extract with calcium precipitate produced a single protein peak shown by polyacrylamide gel electrophoresis. Purified protein exerted maximum growth enhancement at 1 to 2 $\mu\text{g}/\text{ml}$ and was completely lost after treatment with 0.1% trypsin. Protein fractions tended to precipitate at pH lower than 5.0 or in the presence of calcium or magnesium ions. The purified proteins were found to have properties similar to pericellular structural proteins which would indicate that they are responsible for the growth-enhancing activity of conditioned media. It is hypothesized that an understanding of the molecular

and morphological basis for contact or short range interactions affecting proliferation of animal cells must be better understood.

- 5318 5-S-CYSTEINYLDOPA IN THE PLASMA OF MELANOMA PATIENTS AND THE RENAL CLEARANCE OF THIS AMINO ACID. (Eng.) Agrup, G. (Dep. Dermatol., Univ. Gothenburg, Sweden); Andersson, T.; Falck, B.; Persson, K.; Rorsman, H.; Rosengren, A. M.; Rosengren, E. *Acta Derm. Venereol. (Stockh.)* 55(1): 5-6; 1975.

5-S-cysteinyl-dopa was demonstrated in the plasma of two patients with metastases of malignant melanoma and a high excretion rate of 5-S-cysteinyl-dopa in the urine. In one patient the plasma clearance of 5-S-cysteinyl-dopa was 30 ml/min and in the other 69 ml/min. These clearance values were 43 and 45%, respectively, of the creatinine clearance in the two patients. When urinary 5-S-cysteinyl-dopa levels are within normal limits, it is not possible to demonstrate the amino acid in plasma even with methods capable of detecting as little as 25 ng 5-S-cysteinyl-dopa. This suggests that the renal clearance of the amino acid in normal subjects will be similar to that reported here for patients with metastatic melanoma; thus, more sensitive methods may be required for investigation of 5-S-cysteinyl-dopa metabolism in normal subjects.

- 5319 MEASUREMENT OF SERUM FERRITIN BY RADIOIMMUNOASSAY: RESULTS IN NORMAL INDIVIDUALS AND PATIENTS WITH BREAST CANCER. (Eng.) Marcus, D. M. (Albert Einstein Coll. Medicine, Bronx, N.Y. 10461); Zinberg, N. *J. Natl. Cancer Inst.* 55(4):791-795; 1975.

Ferritins are iron-containing proteins found in normal tissues; they increase in concentration in many tumors and the blood of tumor-bearing individuals. A double-antibody radioimmunoassay for measurement of serum ferritin revealed the upper limit of normal as 146 ng/ml for women (mean 34 ng/ml) and 193 ng/ml for men (mean 93 ng/ml). Serum ferritin levels exceeded these limits in pre-operative sera of 41% (14/38) of women with mammary carcinoma (mean 199 ng/ml) and in 67% (65/97) of women with locally recurrent or metastatic mammary carcinoma (mean 671 ng/ml). Individuals with hepatic inflammatory states are known to have high serum ferritin, and ferritin was increased in 43% of patients with hepatitis or cirrhosis (mean 364 ng/ml) and in 13% of patients with ulcerative colitis or gastroduodenal ulcers (mean 106 ng/ml). Measurement of serum ferritin may be useful in evaluation of patients with breast cancer and in monitoring their response to therapy.

- 5320 DYNAMIC STRUCTURE OF CELL MEMBRANES AND THE USE OF LECTINS AS PROBES FOR NORMAL AND NEOPLASTIC CELL SURFACES. (Eng.) Nicolson, G. L. (Salk Inst. Biological Studies San Diego, Calif. 92112). *Proc. Int. Cancer Congr.* 11th.

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^{125}I - and ferritin-labeled plant lectins (concanavalin A, (Con A), and *Ricinus communis* agglutinin, (RCA_I) were used to study the quantity, distribution, and dynamics of the oligosaccharide components on normal hamster BHK fibroblasts, wild-type polyoma-transformed BHK (PyBHK) cells, and temperature sensitive PyBHK cells (ts 3-PyBHK). The cells were incubated with affinity-purified ^{125}I -labeled lectin or with ferritin-lectin. BHK fibroblasts grown at 32 or 39°C were dramatically less agglutinable with Con A or RCA_I than the PyBHK cells. Ts3-PyBHK cells showed BHK-like lectin agglutinability when grown at 39°C, but showed Py-BHK-like lectin agglutinability when grown at the permissive temperature (32°C). Quantitative labeling with ^{125}I -Con A under saturation conditions at low temperature showed no differences in the total number of Con A binding sites on these cells, but labeling with ^{125}I -RCA_I showed differences in the number of RCA_I receptors. BHK and ts3-PyBHK grown at 39°C consistently bound 2-2.5 times more ^{125}I -RCA_I than PyBHK or ts3-PyBHK grown at 32°C. Labeling of ts3-PyBHK cells grown at 32 or 39°C with ferritin-RCA_I at 0-4°C for 15 min resulted in a uniform distribution of ferritin-lectin molecules at the cell surface. However, when the cells were washed after the 0-4°C incubation and incubated further at 20 or 37°C, dramatic lectin-induced redistribution occurred. Ts3-PyBHK cells grown at 32°C were more susceptible to lectin-induced redistribution than cells grown at 39°C. The results indicate that there is no relationship between the total number of cell surface lectin receptors and cell agglutinability; in normal cells grown *in vitro*, lectin agglutinability changes with cell growth.

- 5321 ULTRASTRUCTURAL ORGANIZATION AND BIOCHEMICAL CHARACTERIZATION OF CHROMATIN-RNA-PROTEIN COMPLEXES ISOLATED FROM MAMMALIAN CELL NUCLEI. (Eng.) Bachellerie, J.-P. (Centre de Recherche de Biochimie et de Genetique Cellulaires du C.N.R.S., 118 Route de Narbonne, F-31077 Toulouse-Cedex, France); Puvion, E.; Zalta, J.-P. *Eur. J. Biochem.* 58(2):327-337; 1975.

Extranucleolar elements were isolated from Chinese hamster ovary cell nuclei and characterized by correlative biochemical-ultrastructural studies. These complex structures were shown to retain a supraparticle arrangement closely resembling the organization *in situ* of definite nuclear areas. In particular the morphological RNA-protein species, namely perichromatin fibrils and granules, were detected in association with characteristic regions of chromatin. By autoradiographic experiments, perichromatin fibrils were shown to represent the morphological state of newly formed heterogeneous nuclear RNA (hnRNA). Chromatin-RNA-protein complexes were further fractionated by means of a treatment dissociating the chromatin component. A minor part of DNA, possibly involved in the biosynthesis remained linked to the resulting RNA-protein network.

- 5322 PROGNOSIS AND INCIDENCE OF SEX CHROMATIN IN BREAST CANCER: A PRELIMINARY REPORT. (Eng.) Ghosh, S. N. (Cancer Res. Inst., Bombay, India); Shah, P. N. *Acta Cytol.* 19(1):58-61; 1975.

Two studies, retrospective and prospective were conducted to evaluate the incidence of sex chromatin in cancer tissue from 126 patients with breast cancer. In the prospective study 76 unselected cases were used; smears were made from frozen section tissue, at least 300 cells were counted and the percentage of sex chromatin was noted. Tumors were classified into six groups based on these findings: A: multiple chromocenters; B: 1-9%, C: 10-14%; D: 15-19%; E: 20-29%; and F: over 30%. Seventy percent or greater was considered normal; less than 20% was considered negative and over 20% was considered positive. Sex chromatin was studied in different parts of the tumor in ten cases and in complete histologic preparations in 15 cases, and was found to be consistent with the frozen section data. For the retrospective study, 50 cases with a five year or longer followup were evaluated by study of the old histologic slides. Two hundred cells per slide were counted and tumors were classified according to the above scheme. Correlations between sex chromatin percentages and survival, disease free interval of distant metastasis, lymph node metastasis and size of tumor were attempted. In the prospective study 57 of 76 patients were negative and 19 of 76 were positive; in the retrospective study 30 of 50 were negative and 20 of 50 positive. Of 28 patients with negative sex chromatin, 26 had positive nodes and 2 had negative nodes; of 18 patients with positive sex chromatin 11 had positive and 7 negative nodes. Among the sex chromatin negative group 22 of 25 patients died within five years, but of those in the positive group only four of 11 succumbed within five years. Sixteen of 24 patients in the negative group had a disease free interval of less than two years while the remaining eight had more than two years. Of the 11 cases in the positive group, only one patient had a disease free interval less than two years. These differences are significant. No significant correlation was seen between sex chromatin percentages and tumor size. It is suggested that tumors having high sex chromatin counts have some relation to the biological behavior of the tumor which can then be correlated with prognosis.

- 5323 EVIDENCE FOR A SUBUNIT STRUCTURE OF CHROMATIN IN MOUSE MYELOMA CELLS. (Eng.) McGhee, J. D. (Inst. Molecular Biology, Univ. Oregon, Eugene, Oreg. 97403); Kimmel, C. B. *Chromosoma* 52(2):189-205; 1975.

Evidence for a repeating subunit in the chromatin of mouse myeloma tissue culture cells is presented. If micrococcal nuclease was allowed to digest chromatin as it existed inside intact nuclei isolated from mouse myeloma tissue culture cells, more than 60% of the DNA could be isolated as a homogeneous fragment on a sucrose gradient. Analytical ultracentrifugation indicated that the protected DNA was native, unnicked, and about 140 ± 10 base pairs long. After less extensive nuclease diges-

tion, the protected DNA migrated in gels in lengths which were integral multiples of this 140 base pair "monomer" band. A submonomer band, 105 ± 10 base pairs long, was also detected. Similar digestion patterns were obtained by two different nuclear isolation procedures, even when intact cells were gently lysed directly in the digestion medium. These results confirm and extend the chromatin digestion studies of previous investigators and provide support for a subunit model for eukaryotic chromatin. The single strand specific S1 nuclease did not digest intranuclear chromatin under the conditions used.

- 5324 KINETICS OF HISTONE METHYLATION *IN VIVO* AND ITS RELATION TO THE CELL CYCLE IN EHRLICH ASCITES TUMOR CELLS. (Eng.) Thomas, G. (Institut für Medizinische Strahlenkunde der Universität, D-8700 Würzburg, Versbacher Landstrasse 5, West Germany); Lange, H. W.; Hempel, K. *Eur. J. Biochem.* 51(2):609-616; 1975.

The appearance of methylated lysines in newly synthesized histones from Ehrlich ascites tumor cells was measured during one generation time. Newly synthesized histones were pulse-labeled *in vivo* by L-[^3H]lysine, and the time course of the uptake of label into monomethyl, dimethyl, and trimethyllysine from gel-electrophoretically isolated histones F2a1 and F3 was followed. Methylation starts immediately after histone biosynthesis. It proceeds, however, more slowly than histone synthesis. Both the rate of methylation and the mechanism of methylating in F3 and F2a1 histones differ. F3 methylation can be described by a first-order reaction, *i.e.*, the reaction rate depends only on the concentration of free methylation sites available. Rate constants of approximately 0.21 h^{-1} were found for all three methylation steps. Methylation in the F2a1 histone proceeds more slowly than in F3. The dimethylation step in this fraction can be described by a zero-order reaction with a rate constant which is the reciprocal of the duration of the DNA synthesis phase. Alternatively this step could be correlated with the transition of the cells from the S phase into the G2 phase. By the end of one generation time all methylation sites in all F2a1 and F3 molecules are occupied by methyl groups at a ratio of about 1:3:1 for monomethyl-, dimethyl- and trimethyllysine in the F3 histone. In the F2a1 molecule the methyllysines consist mainly of dimethyllysine.

- 5325 THE PHOSPHORYLATION OF NUCLEAR PROTEINS IN THE REGENERATING AND PREMALIGNANT RAT LIVER AND ITS SIGNIFICANCE FOR CELL PROLIFERATION. (Eng.) Letnansky, K. (Inst. for Cancer Res., Borschkegasse 8a, A-1090 Vienna, Austria). *Cell Tissue Kinet.* 8(5):423-439; 1975.

The phosphorylation of histones in the regenerating and premalignant rat liver was studied. Male Sprague-Dawley rats were partially hepatectomized or sham operated and after various intervals injected ip with $1.8 \text{ mCi } ^{32}\text{P}$ -orthophosphate one hour before sacrifice; in some cases they were also in-

jected ip with 10 mg of cyclic AMP prior to sacrifice. Hepatomas were induced by daily sc injections of *N*-nitrosodiethylamine (10 mg/kg). The nuclear histones were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis; RNAs were extracted with phenol; and the informosomal proteins were isolated using a procedure for the dissociation of ribosomes by EDTA. The phosphorylation of the nuclear proteins was stimulated in both liver regeneration and neoplastic transformation. In the regenerating liver, all main histone fractions were involved in this process, the type of histone phosphorylated appearing to be dependent on the position of the partially synchronized cells within the generation cycle. At a time when most cells were exhibiting maximum heterogeneous (HnRNA) synthesis, histone F2a2 belonged to those fractions with highly stimulated phosphate incorporation. Phosphorylation of this fraction alone was stimulated by cyclic AMP in parallel with a stimulation of HnRNA synthesis. The preneoplastic liver was characterized by oscillating phosphorylation and dephosphorylation reaction of nearly all histone fractions during the first days of *N*-nitrosodiethylamine administration. After two months of carcinogen administration, a 50-150% stimulation of the phosphorylation of the F1 subfractions was observed. The phosphate content of the other histones, however, had returned to the original level. A series of unidentified proteins, which were isolated together with the histones, showed a very similar pattern of phosphorylation. These proteins were primarily of nonhistone origin. It is suggested that some of them may be responsible for the transport of messenger RNA within the cell.

5326 SYNTHESIS OF RNA CONTAINING A METHYLATED BLOCKED 5' TERMINUS BY HELA NUCLEAR HOMOLOGENATES. (Eng.) Groner, Y. (Albert Einstein Coll. of Medicine, Bronx, N.Y. 10461); Hurwitz, J. *Proc. Natl. Acad. Sci. USA* 72(8):2930-2934; 1975.

Since the previously observed enzymatic blocking at the 5' terminus of mRNA might be a post-transcriptional event occurring in the nucleus before mRNA is transported to the cytoplasm, RNA synthesized *in vitro* by HeLa cell nuclei was examined for blocked methylated 5'-terminal structures. HeLa nuclei were incubated with reaction mixtures containing (α - 32 P)-GTP; at 0, 5, 10, 20, and 40 min, unlabeled S-adenosyl methionine or S-adenosyl[methyl- 3 H]methionine was added to the mixture. The reactions were stopped and unlabeled GTP or L-methionine was added before dialysis of the mixture. The nucleic acids were then precipitated and incubated with pancreatic DNase and bacterial alkaline phosphatase. The product of this reaction was extensively digested with RNase T₂ and analyzed by DEAE-cellulose chromatography in 7 M urea (32 P *in vitro*-labeled RNA) or digested with P₁ nuclease followed by bacterial alkaline phosphatase and analyzed by paper electrophoresis (3 H-methyl *in vitro* labeled nuclear RNA). The *in vitro* synthesized RNA contained a variety of blocked methylated 5'-terminal structures that could be grouped into four general types: m⁷GppN^mm...; m⁷TppN^mm^mp...; m⁷GpppN^mm...; and m⁷GpppN^mm^mm...

Both N^m and M^m could be either one of the four 2'-O-methylated nucleosides. The relative amounts of the N^m species were G = 45%, A = 25%, U = 20%, and C = 10%. The results may indicate a role of triphosphate or diphosphate termini in the formation of 5'-blocked termini synthesis.

5327 METHOD OF SELECTIVE INJURY OF CELLS AT DIFFERENT LEVELS OF RNA SYNTHESIS. (Rus.) Polikarpova, S. N. (Inst. Evolut. Biol., Acad. Sci. U.S.S.R., Moscow, U.S.S.R.); Khrushchov, N. G. *Dokl. Akad. Nauk S.S.S.R.* 224(1):216-219; 1975.

The effect of the incorporation of tritiated uridine with high specific activity (5-22.4 Ci/mM) into RNA of cells at different levels of RNA synthesis was studied in Bii dii FAF-28 line Chinese hamster fibroblasts and in human leukocytes. Tritiated uridine, introduced in doses of 100 and 150 μ Ci/ml, caused cell injury in terms of reduced mitotic index and increased frequency of chromatid type chromosomal aberrations in Chinese hamster fibroblasts with high RNA-synthesizing activity. In human leukocytes, the labeling index was significantly higher in S-G₂ phase than in G₀, i.e., without phytohemagglutinin stimulation, and the mitotic index was significantly lower in S-G₂ than when uridine was introduced in G₀ phase. While there were no chromosomal aberrations in lymphocytes incorporating uridine before phytohemagglutinin stimulation, uridine incorporation by stimulated lymphocytes caused high frequency of chromatid type aberrations.

5328 THE DISTRIBUTION AND PROPERTIES OF ASPARTYL TRANSFER RNA IN HUMAN AND ANIMAL TUMORS. (Eng.) Briscoe, W. T. (Scripps Clinic and Res. Foundation, 476 Prospect Place, La Jolla, Calif. 92037); Griffin, A. C.; McBride, C.; Bowen, J. M. *Cancer Res.* 35(9):2586-2593; 1975.

The elution profile of aspartyl transfer RNA (aspartyl-tRNA) from a wide variety of human and animal tumors was studied. Reversed phase two and five chromatography in conjunction with labeled amino-acids (L-[2,3- 3 H]aspartic acid and L-[14 C]-aspartic acid) sampled at regular intervals provided the elution profile. Four isoacceptor peaks were determined. There was a strong positive correlation between the presence of relatively large amounts of aspartyl tRNA_{IV} in hamster simian virus 40 (SV40) induced tumors (4.2-18 pm/A₂₆₀ U of tRNA), as well as in baby hamster kidney 21/clone 13 cells in tissue culture (40-44 pm/A₂₆₀ of tRNA). Human tumors classified as carcinoma and adenocarcinoma contained increased amounts of aspartyl tRNA (2.5-40 pm/A₂₆₀ U of tRNA), while those termed sarcoma, melanoma, and hepatoma did not. Other experiments using labeled aspartic acid tested the anticodon properties of aspartyl tRNA_{IV} against those of aspartyl tRNA in response to random polynucleotides. The results showed that tRNA_{III} and tRNA_{IV} were bound by the ribosomes to about the same degree for a specified codon. An

additional assay measured the ability of each of the four aspartyl tRNA species to transfer [^3H]-aspartic acid into a polypeptide. It was concluded that tRNA_{IV} is fully functional in polypeptide synthesis and must therefore be structurally similar or identical to tRNA_{III} in regions that contain binding sites involved in protein synthesis.

- 5329 COMPARISON OF THE PROPERTIES OF CYTOPLASMIC POLY(ADENYLIC ACID)-CONTAINING RNA FROM POLYSOMAL AND NONPOLYSOMAL FRACTIONS OF MURINE MYELOMA CELLS. (Eng.) MacLeod, M. C. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, Tenn. 37380). *Biochemistry* 14(18):4011-4018; 1975.

The relationship between nonpolysomal and polysomal cytoplasmic poly(A)-containing RNA was characterized in the S-194-C1 2 line of γA immuno globulin-secreting murine myeloma cells. About 40% of the cytoplasmic poly(A)-containing RNA in exponentially growing murine myeloma cells was not found associated with polysomes. This RNA fraction had a size distribution and poly(A) content very similar to that of polysomal poly(A)-containing RNA. In pulse-chase experiments, some, but not all, of the nonpolysomal poly(A)-containing RNA was transferred into polysomes. The kinetics of accumulation of radioactive poly(A)-containing RNA in cytoplasmic fractions were inconsistent with a simple precursor:product relationship between non-polysomal and polysomal poly(A)-containing RNA; alternative models for this relationship are discussed. A common feature of these models is the existence of translational control mechanisms in these cells.

- 5330 HUMAN LEUKEMIC CELLS: CHARACTERISTICS OF MODIFIED METHYLATED MINOR BASES OF LOW MOLECULAR WEIGHT RIBONUCLEIC ACIDS. (Eng.) Wulff, U. C. (Kinderklinik der Medizinischen Hochschule, Lubeck, West Germany); Desai, L. S.; Heuer, R.; Meissner, J.; Foley, G. E. *Exp. Cell. Res.* 90(1): 63-72; 1975.

RNA isolated from cells derived from human leukemia (CCRF-CEM), infectious mononucleosis (CCRF-RKB,SB), and a normal donor (CCRF-SLT) were resolved into four peaks on Sephadex G-100 columns. tRNA (4S or peak IV) showed a higher ratio of 6-methyladenosine, N²,N²-dimethylguanosine, and 5-methylcytosine, in RKB and SB cells as compared with CEM and SLT cells. Striking differences were observed in 7-methylguanosine; there was a 4-5-fold increase in CEM cells, and a two-fold increase in RKB and SB, as compared with SLT cells. The total content of modified minor bases, including pseudo-uridine, showed no significant quantitative differences in the 4.6S-RNA (peak III) RNA. A 3-4-fold increase was seen in the 7-methylguanosine content of 5.5S (peak II) isolated from CEM cells as compared to RKB, SB and SLT cells. 3-Methylcytosine was found only in CEM, and higher ratios of minor bases were found in 5.5S RNA isolated from CEM, as compared with SLT, RKB, and SB cells. These observations are of particular interest in view of increased excretion of methylated purines in urines of patients or animals with cancer, and may reflect increased methylation

reactions and/or increased metabolic turnover of methylated bases in the tumor-bearing host.

- 5331 UNCERTAINTY IN THE DETERMINATION OF THE MOLECULAR WEIGHT OF POLY(A)-CONTAINING RNA. (Eng.) MacLeod, M. C. (Inst. Molecular Biology, Univ. Oregon, Eugene, Oreg. 97403). *Anal. Biochem.* 68(1):299-310; 1975.

Evidence is given that estimates of the weight average molecular weight of mouse myeloma cell cytoplasmic messenger RNA by polyacrylamide-gel electrophoresis and by sucrose gradient sedimentation differ by a factor of 2, and that this difference is due in part to poly(A) sequences. Exponentially growing cultures of the S-194-C1 2 line of IgA-secreting myeloma cells were concentrated to 2×10^6 to 4×10^6 cells/ml in fresh medium and labeled for 2-3 hr with 2,8- ^3H adenosine or 5,6- ^3H uridine. Total cytoplasmic poly(A)(+) RNA was extracted; the extracts were diluted 3-fold with water, brought to 0.1 M Tris (pH 9.0) and 1% sodium dodecyl sulfate, and then extracted with phenol. The final aqueous phase was adjusted to 1% sodium dodecyl sulfate and 0.1 M NaCl, and the RNA was precipitated overnight. The RNA was analyzed by electrophoresis through a 3% polyacrylamide gel or sedimented through a 15-30% sucrose gradient. The weight average molecular weight calculated on the basis of the results of the polyacrylamide gel electrophoresis was 14.1×10^5 , and that calculated on the basis of the sucrose gradient results was 5.97×10^5 . On the average, the weight average molecular weight determined from the sedimentation profiles was smaller by a factor of 2.1 than the molecular weight determined from the electrophoretic profiles. The difference in the weight average molecular weight was neither due to degradation of the RNA during sedimentation nor to acid poly(A) double helix formation during electrophoresis. When synthetic poly(A) was analyzed by sucrose gradient sedimentation, it sedimented as a single peak with a modal sedimentation coefficient of 6.4S. When analyzed by gel electrophoresis, the same preparation gave a wide size distribution with a significant fraction of the radioactivity migrating more slowly than 28S ribosomal RNA. Thus, synthetic poly(A) molecules behaved in a manner qualitatively similar to cytoplasmic poly(A)(+) RNA. The ratio of the electrophoretic molecular weight to the sedimentation molecular weight was about 2 for pulse-labeled poly(A)(+) RNA. For steady-state-labeled poly(A)(+) RNA, however, this ratio was only 1.4. This finding is consistent with the hypothesis that the difference between the molecular weight calculated by the two methods is due, at least in part, to the presence of poly(A) sequences in the RNA molecules.

- 5332 TRANSPORT OF MESSENGER RNA INTO DIFFERENT CLASSES OF MEMBRANE-ASSOCIATED POLYRIBOSOMES IN EHRlich-ASCITES-TUMOR CELLS. (Eng.) Van Venrooij, W. J. (Laboratorium voor Biochemie der Universiteit, Geert Grooteplein Noord 21, Nijmegen, Netherlands); Gielkens, L. J.; Janssen, A. P. M.; Bloemendal, H. *Eur. J. Biochem.* 56(1):229-238; 1975.

The membrane-bound polyribosomes in Ehrlich ascites tumor cells were separated into a loosely bound and a tightly bound fraction by means of a high salt treatment. The fractions were isolated by suspending the membrane pellet in medium containing 500 mM KCl. After centrifugation for ten minutes at 20,000 x g, the supernatant contained the loosely bound polyribosomes, and the pellet contained the tightly bound polyribosomes. The latter were made soluble by suspending the pellet in buffer and adding 0.5 ml of a mixture of 5% sodium deoxycholate and 3% Triton X-100. Both membrane fractions as well as the free polyribosomes in the supernatant were determined on discontinuous sodium dodecyl sulfate gradients to synthesize about the same set of proteins, suggesting a close relationship between these polyribosome fractions in the Ehrlich cell. Relatively high concentrations of cycloheximide (100 µg/ml) did not prevent newly synthesized polyadenylate containing messenger RNA (mRNA) from entering the tightly bound polyribosome fraction. Treatment of the cells with puromycin (1 mM) in the presence of cycloheximide (200 µg/ml), which released about 70% of the nascent chains, had no significant effect on the entrance of newly synthesized mRNA into tightly bound polyribosomes. These results suggest that in Ehrlich ascites tumor cells nascent polypeptide chains are not involved in the binding of polyribosomes to membranes.

- 5333 EFFECT OF POLYCLONAL B-CELL ACTIVATORS ON DNA SYNTHESIS IN FIBROBLASTS. (Eng.) Persson, U. (Div. Immunobiology, Karolinska Inst., Wallenberg Laboratory, Lilla Frescati, 104 05 Stockholm 50, Sweden); Moller*, G. *Scand. J. Immunol.* 4(5/6):527-534; 1975.

To establish whether the effect of different polyclonal B-cell activators (PBA) on nonlymphoid cells was analogous to their effect on lymphocytes, a study was carried out using embryo fibroblasts. Fibroblast cultures were derived from 15- to 18-day-old fetuses of F₁ hybrids of A/Sn mice with CBA, C57BL, or B10.SM strains. The culture medium contained 10% calf serum. PBA tested included *Escherichia coli* lipopolysaccharide, type III pneumococcal polysaccharide, dextran, dextran sulfate, polyvinylpyrrolidone, and pentosan sulfate. DNA synthesis in PBA-treated cultures was based on uptake of ³H-thymidine, and the thymidine-uptake observed with PBA-treated cultures was compared with the background uptake observed with untreated cultures. All PBA caused maximal DNA synthesis in fibroblast cultures 24 hr after addition of the agents, and at 48 hr the effects were significantly smaller. However, increased DNA synthesis after addition of different PBA was not observed in all experiments, and the occurrence of stimulation was determined by the background level of DNA synthesis in the untreated cultures. Thus, cultures with a high background of thymidine uptake usually showed stimulation by PBA, whereas very dense cultures with low backgrounds as a rule did not respond to PBA. Medium from dense, contact-inhibited fibroblast culture was shown to contain an inhibitor that blocked the

stimulatory effect of PBA. Cultures that were not contact-inhibited and that showed a very high background uptake were not stimulated, and often showed a concentration-dependent decreased level of DNA synthesis after the addition of different PBA. When tests were carried out in the absence of calf serum in the culture medium, the addition of PBA failed to activate DNA synthesis. This finding was in direct contrast to that observed with lymphocytes, which respond in the absence of calf serum. The findings thus show that PBA can affect cells other than B lymphocytes, but that the effect is not analogous to that on lymphocytes and is not a direct triggering event but rather an indirect effect causing interference with mechanisms regulating DNA synthesis.

- 5334 THE INDUCTION OF DNA SYNTHESIS IN THE CHICK RED CELL NUCLEUS IN HETEROKARYONS DURING THE FIRST CELL CYCLE AFTER FUSION WITH HeLa CELLS. (Eng.) Johnson, R. T. (Zoology Dept., Univ. of Cambridge, Downing St., Cambridge, England); Mullinger, A. M. *J. Cell Sci.* 18(3):455-490; 1975.

The induction of DNA synthesis in embryonic (4 - 19-day embryos) chick RBC was examined during the first and second cell cycles after fusion with HeLa cells synchronized in different parts of the G₁ and S phases. After fusion, the cells were pulsed with [³H]thymidine (0.2-50 µCi/ml) and, in some experiments, hydroxyurea (10 mM) was added to the incubation medium. DNA synthesis was monitored; the localization of [³H]thymidine in the RBC nuclei was studied by electron microscopy; and the amount of DNA synthesized was determined by Feulgen densitometry. Protein migration in the heterokaryons was also measured after labeling with ³H-labeled amino acid mixture. The data indicated that the rapidity of induction of DNA synthesis in the RBC was inversely related to the age of the embryo and was directly related to the ratio of HeLa cells to chick nuclei in the heterokaryon. DNA synthesis in the chick nucleus was able to continue after the HeLa nucleus left the S-phase and entered the G₂ phase of the cell cycle, although the induction potential of the late S-phase HeLa cell was somewhat lower than that of the early or mid S-phase cell. Less than 10% of the chick DNA was replicated during the first cycle after fusions, and only about 15% of the chick nuclei approached the 4C value of DNA during the second cycle after fusion. The newly synthesized DNA was associated with either the condensed regions of the nucleus or with the boundaries between the condensed and noncondensed regions. The chick chromosomes at the first and second mitoses after fusion were in the form of prematurely condensed chromosomes that were never fully replicated and were often fragmented. DNA synthesis in the chick nucleus was accompanied by an influx of G₁ and S-phase protein from the HeLa component of the heterokaryon. The results indicate that HeLa proteins synthesized during the G₁ and S-phase migrate into the chick nucleus rapidly after the completion of fusion, but the extent to which the proteins constitute the signals for general activation of the RBC is obscure.

- 5335 RAT HEPATOMA CELLS NUCLEOLAR DNA. II. A POSSIBLE MODEL OF NUCLEOLAR DNA ORGANIZATION. (Eng.) Amalric, F. (Centre de Recherches de Biochimie et de Genetique Cellulaires, 118 Route de Narbonne, 31077 Toulouse-Cedex, France); Zalta, J. P. *Nucleic Acids Res.* 2(8):1321-1328; 1975.

Based on experimental data in Zajdela hepatoma ascitic cells, a model of nucleolar DNA organization was established. DNA extracted from purified nucleoli banded homogeneously in CsCl with a density of 1,700. After sonication, three main components appeared with densities of 1,707, 1,700, and 1,690. These fractions constituted 24%, 51%, and 25%, respectively of the total DNA and contained 0.55%, 0.4%, and less than 0.2% of rDNA. They also contained 0-15%, 0%, and 15-0% repetitive sequences, respectively. A scheme of linear organization for the nucleolar DNA in chromatin is proposed based on the existence of three main kinds of DNA segments (I, II, and III). The three classes are linked together in a linear arrangement, and fraction I contains all the DNA of buoyant density 1,707, all the ribosomal cistrons, and all the sequences with a medium degree of reiteration, while fraction II contains the sequences which respond to the action of the periodic acid Schiff test (PAS), and fraction III contains the DNA of buoyant density 1,690 and the sequences with a high degree of reiteration. According to the proposed arrangement of these classes, the PAS-sensitive and non PAS-sensitive fractions are separated and fractions I and III are adjacent to each other. It is proposed that fraction III could play a role in the formation of intranucleolar ramifications from the perinucleolar chromatin; through folding of the DNA molecule, two regions of chromatin containing fraction III could touch and build a super helix. Fraction I, which is situated between two fractions of type III, is localized in a loop-shaped chromatin structure which constitutes the intranucleolar chromatin, and the adjacent type II fractions, which remain at the nucleolar periphery, could be linked to the whole of perinucleolar chromatin.

- 5336 REINITIATION OF DNA SYNTHESIS IN SENESCENT HUMAN FIBROBLASTS UPON FUSION WITH CELLS OF UNLIMITED GROWTH POTENTIAL. (Eng.) Norwood, T. H. (Sch. Med., Univ. Washington, Seattle); Pendergrass, W. R.; Martin, G. M. *J. Cell. Biol.* 64(3):551-556; 1975.

DNA synthesis in post replicative (senescent) human fibroblasts following fusion with Sendai virus to HeLa or SV40-transformed human fibroblasts (SV80) was estimated by autoradiography following ³H-thymidine labeling. The percentage of nuclei labeled with ³H-thymidine was substantially higher in the heterodikaryons than in the old fibroblast monokaryons and homodikaryons. The percentage of labeled cells declined at the later pulse periods in HeLa x old fibroblast crosses but not in SV80 x old fibroblast crosses. No mitotic figures were seen in either of the heterokaryons produced. The thymidine labeling index (percent labeled nuclei) in heteropolykaryons was found to dependent on the ratio of

HeLa cell nuclei to senescent nuclei. The results indicate that, with respect to the index of DNA synthesis measured, the SV80 and HeLa cell phenotypes are dominant over the senescent fibroblast cell phenotypes.

- 5337 THE KINETICS OF SERUM-INDUCED INITIATION OF DNA SYNTHESIS IN BHK 21/C13 CELLS, AND THE INFLUENCE OF EXOGENOUS ADENOSINE. (Eng.) Brooks, R. F. (Salk Inst., Post Office Box 1809, San Diego, Calif. 92112). *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):369-377; 1975.

After the re-addition of serum in the presence of adenosine (25 µM), the entry of quiescent, serum starved BHK 21 cells into DNA synthesis follows first order kinetics after a well defined lag period of eight hr, and with a rate constant dependent on serum concentration. Initiation of DNA synthesis under these conditions can therefore be considered to be a random event occurring with a "Transition Probability" determined by the serum concentration. In the presence of adenosine, the change of Transition Probability following the addition of serum occurs abruptly. In the absence of exogenous adenosine, however, the change of Transition Probability after serum addition appears to be both gradual and bi-phasic. The initial changes in the absence of adenosine, though smaller in magnitude, display a similar dependence on serum concentration to the changes occurring in the presence of the nucleoside. In contrast, the secondary gradual increase of Transition Probability in the absence of added purines exhibits a higher serum requirement. It is suggested that the regulation of Transition Probability by serum involves some purine-dependent process, and that in the absence of an exogenous supply this becomes limited by endogenous synthesis which in turn may be dependent on serum concentration.

- 5338 DNA MEASUREMENTS ON CELL NUCLEI OF NORMAL, PROLIFERATING AND NEOPLASTIC THYROID TISSUES IN RATS. (Eng.) Christov, K. (Natl. Center Oncology, Acad. Medicine, Sofia-56, Bulgaria); Thomas, C.; Sandritter, W. *Neoplasma* 22(3):285-294; 1975.

Nuclear DNA content was measured in three normal, nine hyperplastic, and 16 neoplastic rat thyroid glands. Thyroid hyperplasia and tumor growth were induced after treatment of 28 10-day-old male Wistar rats with X-rays (300 rads in the neck region) and methylthiouracil (1% in drinking water). The animals were sacrificed 20-450 days after the beginning of the experiment, and the DNA content was determined using an integrating microdensitometer. In the control animals, only diploid thyroid epithelial cells were observed. At the stages of diffuse and nodular thyroid hyperplasia, the total DNA content per nucleus indicated for a diploid chromosome number, and only a few cells were hyperdiploid. In the thyroid adenomas and carcinomas a scattering of the diploid region and an increase in the number of hyperdiploid cells was found. Among the various types of thyroid tumors neither

difference in the number of hyperdiploid cells, nor typical pattern of distribution of these cells in the histogram was found. The increased number of hyperdiploid cells in the hyperplastic and neoplastic thyroids suggest an increase in the proportion of the cells entering the cell cycle and does not indicate appearance of a neoplastic stemline.

5339 NASCENT DNA FROM PHYTOHEMAGGLUTININ-STIMULATED HUMAN LYMPHOCYTES. (Eng.)

Mendelsohn, J. (Univ. California, San Diego, Sch. Medicine, La Jolla, Calif. 92037); Fox, R. M.; Goulian, M.; Barbosa, E. *Immunol. Commun.* 4(4): 373-385; 1975.

A study was carried out with human blood lymphocytes to determine whether unique mechanisms and/or molecular species are involved in DNA synthesis stimulated by phytohemagglutinin (PHA). Cells suspended in complete MEM culture medium were incubated for 60 hr at 37 C with 10 μ l/ml Difco PHA-P. The PHA-treated lymphocytes were next collected by centrifugation, resuspended in Tris buffer containing Mg^{++} and glucose, and reincubated with [3H]-thymidine at 27 C for varying time intervals. The low temperature of incubation slowed the thymidine incorporation and permitted closer observation of early events in DNA synthesis. The reaction was terminated by lysis with sodium dodecyl sulfate or sodium dodecyl sarcosinate and nucleases were eliminated by digestion with pronase. Labeled nascent DNA was isolated from lysates by centrifugation on sucrose gradients, precipitation with acid, and location of fractions by measurements of radioactivity; or by hydroxylapatite chromatography, using a linear gradient of phosphate buffer for elution and recovery of single-stranded DNA at a mean phosphate concentration of 0.18 M, doublestranded DNA at a concentration above 0.25 M. The nascent DNA was identified as the single-stranded species by its sedimentation rate of 4-5 S in sucrose gradients and appeared to be the precursor to chromosomal DNA, as revealed by results of pulse-chase experiments. Thymidine incorporation into the single-stranded DNA fraction reached maximum levels in less than 30 sec of incubation, at which time 64% of the label was in a single-stranded species. With increasing duration of incubation, the level of labeled single-stranded DNA remained constant, whereas an increasing amount of labeled DNA accumulated in the double-stranded fraction. It was concluded that synthesis of DNA by PHA-stimulated lymphocytes involves a low molecular weight, single-stranded, short-lived intermediate similar to that described for other eukaryotic cells.

5340 INTRA- AND EXTRACELLULAR CALCIUM IN EHRLICH ASCITES TUMOR CELL. (Eng.)

Anghileri, L. J. (Innere Klinik und Poliklinik (Tumorforschung) Klinikum der GHS Essen, D-4300 Essen, Hufelandstr. 55, West Germany). *Arch. Geschwulstforsch.* 45(3):219-231; 1975.

Calcium concentration in intra- and extracellular fluid from Ehrlich ascites tumors was compared and the type of molecules which appear to be involved

in its binding were investigated. NMRI mice bearing Ehrlich ascites tumor were injected ip with 10 μ Ci [^{45}Ca]Cl₂, with 10 μ Ci [^{32}P]-orthophosphate, or with 50 μ Ci [^{35}S]-sodium sulfate. Groups of six animals injected with ^{45}Ca or ^{32}P were sacrificed 48 hr after injection, the ascitic fluid was collected, and centrifuged. Samples of ascitic fluid supernatant and of cytoplasm were fractionated through a Sephadex G-200 gel column and the radioactivity and UV absorption measured in each eluted fraction. The molecular characteristics of the distribution pattern were studied by precipitating samples of the supernatants with 10% trichloroacetic acid or with 80% ethanol, dialyzed against distilled water, or passed through an anion- or cation-exchange resin. The phospholipids from the trichloroacetic acid-insoluble fraction were extracted and the ^{32}P -labeled RNA present in this insoluble estimated by measuring the radioactivity released after incubation with RNase. The animals injected with ^{35}S -sodium sulfate were sacrificed 72 hr after injection and processed as the ^{45}Ca and ^{32}P -labeled cells. An aliquot of the cell suspension was also submitted to subcellular fractionation and uronic acid, hexosamine, and ^{35}S in acid mucopolysaccharides determined in each subcellular fraction. The total calcium in the Ehrlich ascites cells was 3.1 μ M/g, wet weight. The cytoplasm contained 24.1% of the cell calcium, 54.6% of the cell magnesium, and 65.9% of the cell phosphorus. Approximately the same amount of ^{45}Ca and ^{32}P in the ascitic fluid supernatant was non-dialyzable. The ion-exchange study indicated that while the total ^{45}Ca was ionizable, 30% of the ^{32}P was not. The distribution of the ^{32}P label in the trichloroacetic acid-insoluble fraction showed very significant differences in phospholipids and in RNA. The cytoplasm had a higher incorporation in phospholipids and RNA than the ascitic fluid supernatant. Gel filtration indicated that most of the calcium in the ascitic fluid supernatant was in ionic form while a considerable amount was protein-bound in the cytoplasm. The cytoplasm also incorporated much more ^{32}P in the macromolecular fraction than the ascitic fluid supernatant; this incorporation was accompanied by a higher DNA and phospholipid concentration. After subcellular fractionation, most of the ^{35}S -labeled mucopolysaccharides were seen in the sediment of 105,000 g. This fraction also contained a great amount of the cell hexosamine and the largest amount of cellular ^{45}Ca bound to particles. It is suggested that the high extracellular calcium concentration observed in ascites cells might produce irreversible changes in the cell membrane physiological function.

5341 STEREOSPECIFIC ANALYSIS OF HEPATOMA, HOST LIVER, AND NORMAL RAT LIVER TRIGLYCERIDES FROM ANIMALS ON CHOW AND FAT FREE DIETS. (Eng.)

Wood, R. (Univ. Missouri Sch. Medicine, Columbia, Mo. 65201). *Lipids* 10(7):404-408; 1975.

Triglycerides from normal liver, host liver, and 7288CTC hepatoma of rats maintained on chow and fat-free diets (4-5 wk) were subjected to stereospecific analysis. Triglycerides were resolved from other neutral lipids by thin layer chromato-

graphy on adsorbent layers of Silica Gel G developed in a solvent system of hexane-diethyl ether-acetic acid. The stereospecific analysis was scaled for 3-5 mg quantities, plus analysis of both 1,2- and 1,3-diglycerides. Normal and host liver triglycerides from animals on the same diet did not exhibit significant differences. Fat-free diet reduced polyunsaturated fatty acids in normal and host liver triglycerides, but had no effect upon hepatoma triglycerides. Each position of hepatoma and liver triglyceride glycerol exhibited a characteristic fatty acid composition. Palmitate concentrations were reduced dramatically, and stearate levels were increased significantly at the 1 position of hepatoma triglycerides, relative to the corresponding position of liver triglycerides which were affected little by diet of tumor. Except for higher percentages of C-20 and higher fatty acids, common to all three positions, the composition of hepatoma triglycerides at the 2 position appeared normal. The 3 position of hepatoma triglycerides contained significantly higher percentages of stearate than liver. Data obtained previously for Ehrlich ascites cell triglycerides were in good agreement with this hepatoma. Data from these two neoplasms suggest that the metabolic system that regulates or controls the fatty acid composition at the 1 and 3 positions of normal tissue triglycerides does not function normally in neoplasms.

- 5342 LIPIDS OF CULTURED HEPATOMA CELLS: VII. STRUCTURAL ANALYSES OF GLYCEROLIPIDS IN MINIMAL DEVIATION HEPATOMA 7288C. (Eng.) Wiegand, R. D. (Univ. Missouri Sch. Medicine, Columbia, Mo. 65201); Wood, R. *Lipids* 10(9):548-554; 1975.

The positional analyses and structure of glyceride species of triglyceride (TG), phosphatidylcholine (PC), and phosphatidylethanolamine (PE) isolated from minimal deviation hepatoma 7288C cells cultured on varying levels of serum, are described. Arachidonic acid at the 2-position of PC was 10.3% when the medium was supplemented with 20% bovine serum and 3.9% when the serum supplement was 50%. No other marked effects of serum level were found. Percentage composition of fatty acids esterified at each position of the three glycerolipids was different, indicating a nonrandom distribution of acyl groups in triglycerides and the two diacyl phosphatides. The carbon number distribution of diglycerides from PE and PC did not agree with the calculated 1-random, 2-random diacyl distribution, indicating pairing of certain acids in the diglycerides derived from these phospholipid classes. The determined triglyceride carbon number distributions suggested preferential pairing of some acids in this lipid class. The 1-, 2-diglycerides derived from PC, PE, and TG differed, indicating either selectivity in utilization of diglyceride species in biosynthesis of these glycerolipids, or modification of glycerolipids after their initial synthesis.

- 5343 SOME BIOCHEMICAL CHARACTERISTICS OF RAT LIVER AND MORRIS HEPATOMA NUCLEI AND NUCLEAR MEMBRANES. (Eng.) Spangler, M. (Univ. Pittsburgh Sch. Medicine, Pittsburgh, Pa. 15261); Coetzee, M. L.; Katyal, S. L.; Morris, H. P.; Ove, P. *Cancer Res.* 35(11/Part 1):3131-3145; 1975.

Biochemical characteristics of nuclei prepared from host liver (male Buffalo rats) and from Morris hepatomas 7777 and 7800 were compared. Several criteria including equal specific activity ratios (homogenate:nuclei) for several marker enzymes were used to ensure that liver and hepatoma nuclei were of equal purity. Phospholipids, proteins, and sialic acid content were compared in liver and hepatoma sucrose nuclei and in membrane and chromatin fractions obtained from liver or hepatoma nuclei. As determined by sodium dodecyl sulfate polyacrylamide electrophoresis, the only qualitative difference in protein that could be detected was in 2 of the 4 nuclear fractions. There was an extra band in each of the two hepatoma fractions. Sialic acid was increased in hepatoma nuclei. A fraction containing most of the inner nuclear membrane from liver nuclei had no sialic acid, whereas the equivalent hepatoma fraction did have sialic acid. Total phospholipids were increased in hepatoma nuclei. This increased phospholipid concentration in hepatoma nuclei as compared to liver nuclei was apparent with sucrose nuclei, citric acid nuclei, membrane-denuded nuclei, chromatin, and nuclear fractions. Determination of the percentages of individual phospholipids making up the total phospholipids extracted revealed that the only significant change in the phospholipid composition of hepatoma nuclei was an increase in sphingomyelin. A large amount of this sphingomyelin was found to be associated with chromatin. The possible significance of chromatin-associated phospholipids is discussed.

- 5344 PRIMARY CULTURE OF PARENCHYMAL LIVER CELLS ON COLLAGEN MEMBRANES: MORPHOLOGICAL AND BIOCHEMICAL OBSERVATIONS. (Eng.) Michalopoulos, G. (The Medical Sch., Univ. Wisconsin, Madison, Wis. 53706); Pitot, H. C. *Exp. Cell Res.* 94(1):70-78; 1975.

The morphology of cells and the inducibility of tyrosine aminotransferase (TAT) were examined in nondividing primary cultures of freshly-prepared adult rat liver cells. The cells were maintained for long periods either on collagen-coated Petri dishes or on the surfaces of collagen gels that are loosened after six hours from their attachment to the sides of the Petri dishes. In the latter instance, the cells on the surface of the gel, which floats in supplemented L-15 culture medium, approach one another and after five days come to form a continuous epithelioid monolayer. The diameter of the gel correspondingly contracts from 60 mm to 10 mm. This contraction requires the physical presence of the cells. The cells in the monolayer oppose one another with straight line junctions, and structures resembling bile canaliculi are observed. The cells assume a square or polygonal shape. As evidenced by changes in the DNA content of the gels, the number of cells decreases for the first five days to about 40% of the initial number, but remains constant thereafter. Dead cells are easily separated from the gels by the agitation produced by changing the fluid culture medium, which is replaced daily.

TAT activity may be significantly induced by 10^{-5} M hydrocortisone or 10^{-4} M dibutyryl-cyclic AMP in cells maintained in this fashion for up to three weeks, whereas cells maintained on collagen-coated plates retain TAT inducibility for only 6-8 days. The continued presence of insulin (0.5 μ g/ml) is necessary both for the formation of monolayers and for the induction of TAT. The culture of liver cells on floating gels permits the study of liver functions in a model *in vitro* system where the cells do not exhibit a rapid decline in function.

- 5345 FATTY ACID SYNTHETASE FROM A MOUSE MAMMARY ADENOCARCINOMA. (Eng.) Lin, C. Y. (Children's Hosp. Medical Center Northern California, Oakland, Calif. 94609); Smith, S.; Abraham*, S. *Cancer Res.* 35(11/Part 1):3094-3099; 1975.

Fatty acid synthetase was isolated from transplantable mammary adenocarcinomas carried by C3H mice. Comparison of physicochemical and immunological properties of this enzyme with those of the fatty acid synthetase isolated from normal glands of lactating C3H mice indicated that the enzymes are similar in all respects. Both the tumor and the normal gland appeared to contain antigenically equivalent fatty acid synthetases of comparable catalytic activity. The enzymes isolated from lactating mammary glands and from the mammary adenocarcinoma utilized acetyl-coenzyme A and butyryl-coenzyme A equally well as primer for fatty acid synthesis. Approximately 12% of the activity of the enzymes from tumor and normal glands was observed in the absence of any primer, indicating that both enzymes contained some malonyl-coenzyme A decarboxylase activity. The products of the purified fatty acid synthetase from normal and neoplastic tissues were the same, mainly long-chain fatty acids. The normal gland contained 30 times more enzymes per gram tissue than did the neoplasm; this may account in part for the relatively low rate of fatty acid synthetase found previously in this neoplasm.

- 5346 UPTAKE OF ^{67}Ga IN THE REGENERATING RAT LIVER AND ITS RELATIONSHIP TO LYSOSOMAL ENZYME ACTIVITY. (Eng.) Hammersley, P. A. G. (Royal Marsden Hosp., Sutton, Surrey SM2 5PT, England); Cauchi, M. N.; Taylor, D. M. *Cancer Res.* 35(5):1154-1158; 1975.

The uptake of ^{67}Ga citrate was studied in regenerating Marshall rat liver over a period up to 72 hr after partial hepatectomy. The ^{67}Ga concentration at three hours after hepatectomy was about three times that found in normal liver; the concentration then fell to a minimum at the peak of DNA synthesis before increasing to a maximum of four times the normal liver value at 42 hr. This increase was related to lysosomal enzyme activity rather than to specific phases of the cell cycle, there being a highly significant correlation ($p < 0.001$) with aryl sulfatase activity. In both regenerating and normal rat livers, ^{67}Ga uptake was reduced when protein synthesis was inhibited by cycloheximide but was unaffected by inhibition of DNA synthesis by cytosine arabinoside. These re-

sults are consistent with the variation of ^{67}Ga uptake with time after hepatectomy. After DNA synthesis and mitosis, there is renewed protein (including lysosomal enzyme) synthesis; also, the enhanced concentration of ^{67}Ga three hours after hepatectomy occurs in a period of rapid protein and ribosome synthesis.

- 5347 DEGRADATION OF POLY(ADENOSINE DIPHOSPHATE RIBOSE) BY HOMOGENATES OF VARIOUS NORMAL TISSUES AND TUMORS OF RATS. (Eng.) Miwa, M. (Inst. Med. Sci., Univ. Tokyo, Japan); Nakatsugawa, K.; Hara, K.; Matsushima, T.; Sugimura, T. *Arch. Biochem. Biophys.* 167(1):54-60; 1975.

The degradation of poly(ADP-ribose) by various normal tissues and transplantable tumors was studied in Donryu and Buffalo strain rats. The tissues and tumors were homogenized and added to an incubation mixture containing 3 nM of ADP-ribose residues of [^{14}C]poly-(ADP-ribose), 3 μ M sodium phosphate buffer (pH 7.5), and 0.6 μ M 2-mercaptoethanol. After incubation at 37 C for ten min, 20 μ l of the mixture were applied to a filter paper disc to determine the acid-insoluble radioactivity. The rest of the incubation mixture was heated in a boiling water bath for two min, and centrifuged at 10,000 rpm for five min; the supernatant was mixed with authentic markers, and aliquots were subjected to paper chromatography and thin-layer chromatography. The testis had the highest activity (4.41 U/mg protein) of the tissues examined. The kidney, thymus, intestinal mucosa and spleen showed fairly high activities, while other organs had moderate or low activities; the serum had essentially no activity. Rapidly growing Yoshida ascites hepatomas had higher activities (1.34 - 1.81) than normal liver (0.85); slow-growing Morris hepatomas had almost the same activities (0.91 - 0.93) as that of normal liver. The major pathway of degradation of poly-(ADP-ribose) in all tissues was through poly-(ADP-ribose) glycohydrolase. Phosphodiesterase was of minor importance in hydrolysis of poly-(ADP-ribose). These findings suggest the importance of poly-(ADP-ribose) glycohydrolase both in normal and tumor tissues for the rapid turnover of poly(ADP-ribose).

- 5348 KINETIC STUDIES ON RAT LIVER AND BEEF HEART MITOCHONDRIAL ATPase: EVIDENCE FOR NUCLEOTIDE BINDING AT SEPARATE REGULATORY AND CATALYTIC SITES. (Eng.) Schuster, S. M. (Inst. for Enzyme Res., Univ. Wisconsin, Madison, Wis. 53706); Ebel, R. E.; Lardy, H. A. *J. Biol. Chem.* 250(19):7848-7853; 1975.

Mitochondrial ATPases from rat liver and beef heart were used to study the effects of guanylylimidodiphosphate (GMP-P(NH)P) and adenylylimidodiphosphate (AMP-P(NH)P) on the kinetics of MgATP, MgITP, and MgGTP hydrolysis. AMP-P(NH)P was a noncompetitive inhibitor of hydrolysis of all substrates with the rat liver enzyme, whether activating anions were present or not. Also with the liver enzyme, AMP-P(NH)P caused only MgATP hydrolysis to appear to have positive cooperativity. With the beef heart enzyme, AMP-P(NH)P was a competitive inhibitor of

ATPase activity and caused positive cooperativity; it gave noncompetitive patterns with GTP or ITP as substrates. In both enzyme systems, GMP-P(NH)P gave complex inhibition patterns with MgATP as the substrate, but was a competitive inhibitor of MgITP and MgGTP hydrolysis. These results support the existence of two types of nucleotide binding sites, with varying degrees of specificity and interaction on the ATPase molecules from both sources. It is postulated that MgATP and AMP-P(NH)P bind to the regulatory site while MgATP, MgGTP, MgITP, and GMP-P(NH)P bind to the catalytic site.

5349 MORPHOLOGICAL DIFFERENTIATION OF CULTURED MOUSE GLIOBLASTOMA CELLS INDUCED BY DIBUTYRYL CYCLIC ADENOSINE MONOPHOSPHATE. (Eng.)

Sato, S. (Inst. Medical Science, Univ. Tokyo, P. O. Takanawa, Tokyo, Japan); Sugimura, T.; Yoda, K.; Fujimura, S. *Cancer Res.* 35(9):2494-2499; 1975.

A culture line of mouse glioblastoma cells changed morphologically to differentiated astrocyte-like cells when cultured in medium with dibutyryl cyclic adenosine monophosphate (DBcAMP) and theophylline. Morphological alteration occurred within only five hours when 3 mM DBcAMP and 1 mM theophylline were used, and in one day when 1 mM DBcAMP and 1 mM theophylline were used. Cells showing this morphological change reverted completely to immature cells when they were transferred to medium without these two chemicals. Addition of 1 or 3 mM dibutyryl cyclic guanosine monophosphate with 1 mM theophylline to the medium also induced development of cytoplasmic processes from these cells; the cells became stellate, although the cytoplasmic processes were not as long or as numerous as those induced by DBcAMP, and the altered cells could not be referred to as differentiated glia cells. Sodium butyrate (3 mM) induced morphological alterations similar to those induced by dibutyryl cyclic guanosine monophosphate, but fewer cells showed these alterations. Addition of cAMP or cyclic guanosine monophosphate in the presence of theophylline or addition of theophylline alone did not induce morphological changes of the cells. The results demonstrate that cultured mouse glioblastoma cells, which maintain the biochemical markers of glia cells but do not show the morphology of mature glia cells either *in vivo* or in culture, change morphologically into cells like mature glia cells when cultured in medium with DBcAMP.

5350 CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE PHOSPHODIESTERASE ACTIVITY IN MALIGNANT AND CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE-INDUCED "DIFFERENTIATED" NEUROBLASTOMA CELLS. (Eng.)

Kumar, S. (Univ. Colorado Med. Cent., Denver); Becker, G.; Prasad, K. N. *Cancer Res.* 35(1):82-87; 1975.

The regulation of cyclic AMP phosphodiesterase activity in homogenates of malignant and cyclic AMP-induced "differentiated" neuroblastoma cells was studied. Malignant neuroblastoma cells of at least three mouse and one human clone had both the low (2-4 μ M) and the high (66-106 μ M) K_m phospho-

diesterases. In cyclic AMP-induced differentiated cells, the K_m values were slightly decreased and the V_{max} values were slightly increased in comparison to malignant cells. Magnesium and manganese stimulated phosphodiesterase activity in both malignant and differentiated cells, while EDTA completely inhibited enzyme activity in both types of cells. Calcium, zinc, copper, mercury, and imidazole only partially reduced enzyme activity in malignant cells but completely inhibited the activity in differentiated cells. The pH optimum for phosphodiesterase activity was about 8 in both malignant and differentiated cells. The quantitatively different effects of divalent ions on phosphodiesterase activity in malignant cells, together with differences in K_m and V_{max} , suggest that there is a change in the regulation of phosphodiesterase activity during malignant transformation of nerve cells.

5351 DIFFERENTIATION AND CHARACTERIZATION OF THE CYTOPLASMIC AND NUCLEAR DEOXYRIBONUCLEIC ACID POLYMERASES FROM BABY HAMSTER KIDNEY CELLS. (Eng.)

Lazarus, L. H. (Neuroendocrinology Lab. Salk Inst., P.O. Box 1809, San Diego, Calif. 92112); Kitron, N. *Biochim. Biophys. Acta* 402(3): 309-322; 1975.

Distinct DNA polymerase activities were found in the cytoplasmic and nuclear fractions of a baby hamster kidney cell line. They were separated by chromatography on DEAE-cellulose and partially purified by ammonium sulfate fractionation, DNA-cellulose and linear sucrose gradients. The cytoplasmic DNA polymerase exhibited a sedimentation-coefficient of 6.95S in 0.15 M NaCl, and its activity was highly sensitive to inhibition by *N*-ethylmaleimide (0.01-1.0 mM) and elevated temperatures (95% inactivation after one minute at 60 C), regardless of the presence of DNA template or other cofactors. It was stimulated by monovalent salts in the order of $NH_4Cl > KCl > NaCl > CsCl > LiCl$ (inhibitory). The DNA polymerase extracted from nuclei sedimented with a sedimentation coefficient of 3.47S, was resistant to inactivation by *N*-ethylmaleimide, and maximally stimulated by NaCl, while also being inhibited by LiCl. For optimal activity, both DNA polymerase activities required a divalent cation, with $MgCl_2$ being more effective than $MnCl_2$. Although the optimal pH values for the two enzyme activities differed slightly, glycine NaOH buffer induced an alkaline shift of 1.5 pH units in the optimum of both enzymes. This was accompanied by an increase in the effectiveness of $MnCl_2$ relative to $MgCl_2$ for the cytoplasmic DNA polymerase.

5352 DNA POLYMERASE ENZYMES IN NORMAL AND NEOPLASTIC GROWTH. (Eng.)

Chiu, J.-F. (M.D. Anderson Hosp. and Tumor Inst., Houston, Tex.); Craddock, C.; Morris, H. P.; Hnilica, L. S. *Cell Cycle in Malignant Immunology, Proc. Annu. Hanford Biol. Symp., 13th.* Richland Washington, D. C., U.S. Energy Research and Development Administration, 1975, pp. 119-131.

The activities of nuclear DNA polymerases were

investigated in normal and neoplastic growth. A high-molecular weight 6-8 S bound form DNA polymerase activity was found in fetal and neonatal livers of male Sprague-Dawley rats and in several Morris hepatomas. The 6-8 S DNA polymerase activity of the Morris hepatomas could be directly correlated to their degree of differentiation and growth rates. However, there was only marginal activity detectable in the nuclei of regenerating rat liver. The activities of nuclear DNA polymerase enzymes were also investigated in Fisher rats maintained on a hepatocarcinogenic diet of *N,N*-dimethyl-*p*-(*m*-tolylazo-aniline) (3'-MDAB, 0.06%, for 8, 32, and 104 days). The 6-8 S bound form DNA polymerase activity appeared in the liver about two weeks after the introduction of 3'-MDAB, increased considerably, and reached a prominent maximum between 30 and 40 days of the diet. After 40 days, this DNA polymerase activity decreased gradually. No similar enzyme could be detected in control rats or in rats maintained on a diet of a noncarcinogenic hepatotoxin α -naphthyl-isothiocyanate (0.05%, for 8, 42, and 65 days). These studies are in good agreement with previous data in showing that certain embryonal genes normally inactive in adult liver are reactivated in hepatomas.

5353 ISOLATION AND CHARACTERIZATION OF NUCLEAR RNA POLYMERASE II FROM CHICKEN MYELOBLASTOSIS CELLS. (Eng.) Chuang, R. Y. (Duke Univ. Med. Cent., Durham, N. C.); Chuang, L. F.; Laszlo, J. *Cancer Res.* 35(3):687-693; 1975.

RNA polymerase II was isolated from chicken myeloblastosis and bone marrow cells, and its properties and the effects of metal ions and several inhibitors upon it, were reported. Cells in suspension were disrupted and intact cell nuclei were isolated. Following incubation for 30 min. at 37 C, reactions were stopped and RNA polymerase activity was determined. Purification of the solubilized enzyme through a diethylaminoethyl-Sephadex A-25 column resolved a minor peak and two major peaks of enzyme activity designated peaks I, II_a and II_b, resp., with regard to their sensitivity to α -amanitin inhibition. The α -amanitin-sensitive activities (II_a and II_b) represented over 97% of total enzyme activity from myeloblastosis cells but a smaller percentage in enzyme from bone marrow cells. Total RNA polymerase activity (I + II_a + II_b) was also about ten times less in bone marrow preparations. The RNA polymerase peaks II_a and II_b were further purified by glycerol gradient centrifugation. The activities of these purified peaks were shown to require the presence of all four nucleoside triphosphates, to depend upon an exogenous source of DNA, to be sensitive to DNase, to be inhibited by *N*-ethylmaleimide, and to yield an RNase-sensitive product. The enzymes required Mn^{2+} for activity, partially replaceable with Mg^{2+} . Mg^{2+} was seen to be inhibitory with optimal Mn^{2+} concentrations, though, suggesting competition. II_b was more sensitive to Mg^{2+} than II_a. Arabinoside cytosine triphosphate (ara-CTP) was shown to completely inhibit the purified RNA polymerases, but the less purified enzymes were more resistant. Rifamycin SV affected the purified enzymes slightly at very high concentra-

tions and cycloheximide had no effect. The major activities of RNA polymerase from chicken myeloblastosis cells were similar to reported nuclear polymerase II activities from eukaryotic cells. Lack of rifamycin SV or cycloheximide inhibition suggested that II_a and II_b were of nucleoplasmic origin. It was suggested that the increase of RNA polymerase II activity in myeloblastosis cells, correlated with the previously noted increased levels of nucleoplasmic RNA synthesis in cells infected by leukemic virus. Also, the sensitivity of the enzyme to ara-CTP was felt to play a possible role in the known inhibition of cell growth associated with ara-CTP.

5354 THE PRESENCE OF AN INHIBITOR OF tRNA SULFURTRANSFERASE IN MORRIS HEPATOMAS. (Eng.) Wong, T.-W. (Dept. Pathology, Univ. Chicago, Chicago, Ill. 60637); Harris, M. A.; Morris, H. P. *Biochem. Biophys. Res. Commun.* 65(3):1137-1145; 1975.

A transfer RNA (tRNA) sulfurtransferase was isolated from the 160,000 $\times g$ supernatant of Buffalo rat liver and a number of Morris hepatomas. This enzyme was shown to catalyze the transfer of labeled sulfur from [³⁵S]β-mercaptopyruvate to tRNA in the presence of ATP (1 μM) and Mg^{2+} (3 μM $MgCl_2$). All six Morris hepatomas examined (9618A₂, 7777, 5123TC, 7800, 5123B, and 7787) had a lower specific activity of tRNA sulfurtransferase than their host liver or normal liver. The decrease in enzyme activity was roughly proportional to the growth rates of the tumors. The faster the growth rate, the greater the decrease in tRNA sulfurtransferase activity. Studies with a hepatoma of fast growth rate (9618A₂), and of intermediate growth rate (5123B), showed that the enzyme activity in the host liver supernatant could be suppressed by the addition of tumor supernatant, suggesting that the lower enzyme activity was due in part to the presence of an inhibitor in the tumor supernatants. Studies with the Morris hepatoma 5123TC using column chromatography indicated that the inhibitor was dialyzable and heat-stable, with a molecular weight below 5,000. For the slow-growing hepatoma 7787, no inhibitor was found in the cytosol, suggesting that in this instance, the decrease in activity was due solely to a lower enzyme level in the tumor.

5355 GALACTOSYLTRANSFERASE ACTIVITIES IN HUMAN SERA: DETECTION OF A CANCER-ASSOCIATED ISOENZYME. (Eng.) Podolsky, D. K. (Harvard Medical Sch., Boston, Mass.); Weiser, M. M. *Biochem. Biophys. Res. Commun.* 65(2):545-551; 1975.

Sera from normal subjects and cancer patients were evaluated for galactosyltransferase activity including kinetic and electrophoretic properties. Discontinuous polyacrylamide electrophoresis of whole sera demonstrated the presence of an additional peak of enzyme activity in cancer sera. The majority of recovered enzymatic activity in both normal and cancer sera ran as a broad band of activity behind an albumin standard; the cancer-associated peak was slower moving. The slower moving peaks were detected in over 20 patients

with colonic, pancreatic, and gastric carcinoma. This peak was not detectable unless gel reagents were first recrystallized; this may be explained by an overall decrease in recovery of galactosyltransferase activity from gels made with unpurified reagents.

- 5356 CELL SURFACE SIALOGLYCOPEPTIDE METABOLISM AND SURFACE GLYCOSYL TRANSFERASE ACTIVITY IN THE EHRlich ASCITES CELL. (Eng.) Irwin, D. (Dept. Medicine, Queen's Univ., Kingston, Ontario, Canada); Anastassiades, T. P. *Can. J. Biochem.* 53(8):895-902; 1975.

The incorporation of radioactive precursors, both *in vivo* and *in vitro*, into acid insoluble material of whole cells and trypsin or papain labile glycopeptide from the surface of intact cells was studied in Ehrlich ascites cells which were maintained as ip suspensions in Swiss white mice. The *in vivo* incorporation of radioactivity from [³H]glucosamine into a trypsin-labile, cell surface sialoglycopeptide fraction was studied with and without puromycin pretreatment. Tumor-bearing mice were given 5 μ Ci each of [³H]glucosamine and [¹⁴C]valine, ip. Three hours later tumors were removed, trypsinized, the acid soluble portion of the supernatant was lyophilized after removal of trichloroacetic acid, and the water soluble portion was applied on a Sephadex G-50 column and eluted with water. Three ml fractions were collected, 260 nm absorption was measured and portions were counted and analyzed for sialic acid and protein. The results indicated a much more complete inhibition of incorporation into the surface sialoglycopeptide fraction than in the average intracellular acid insoluble glycoproteins. No evidence of turnover of the carbohydrate portion of the surface sialoglycopeptide fraction independent of protein synthesis could be obtained. For the *in vitro* experiments, 50 ml washed cells were suspended in 100 μ l Dulbecco's medium, labeled precursor was added in a vol of 5 μ l normal saline (0.05 or 0.1 μ Ci uridine 5'-diphosphate-N-acetyl-glucosamine or 0.10 μ Ci cytidine 5'-monophosphate (CMP)-N-acetyl neuraminic acid), and the cells were incubated for either 0 or 30 min. Incubation was terminated by adding 2 ml ice-cold Krebs-Ringer II. Cells were washed two times and trypsin (10 mg/ml packed cells) or plain buffer was added and the mixture incubated for 5 min at 22 C. The cells were centrifuged and the supernatant processed for sialoglycopeptide and the pellet precipitated by trichloroacetic acid and prepared for liquid scintillation counting. There was some incorporation of the precursors, largely into acid insoluble material, suggesting the presence of glycosyl transferase activity at the surface. Neuraminidase pretreatment of intact cells stimulated incorporation of the labeled CMP-sialic acid six-fold; almost all of the incorporated counts could be released by subsequent neuraminidase treatment. A much greater proportion of the incorporated counts could be released by papain than by trypsin treatment of the intact cells. It is suggested that the surface acceptor for exogenously added CMP-sialic acid is not identical to the endogenously synthesized trypsin labile surface sialoglycopeptide fraction.

- 5357 DECREASED 6-MERCAPTOPURINE RETENTION BY TWO RESISTANT VARIANTS OF MOUSE NEUROBLASTOMA WITH NORMAL HYPOXANTHINE-GUANINE-PHOSPHORIBOSYLTRANSFERASE ACTIVITIES. (Eng.) Baskin, F. (Southwestern Medical Sch., Dallas, Tex. 75235); Rosenberg, R. N. *J. Pharmacol. Exp. Ther.* 193(1):293-300; 1975.

Two mouse neuroblastoma variants whose growth in tissue culture is resistant to 6-mercaptopurine (6-MP) were characterized as part of an effort to devise more effective chemotherapeutic regimens for the treatment of neuroblastomas. The 6-MP concentrations required for 50% inhibition of the growth rates of the two variants are 110- and 575-fold higher, respectively, than that required for inhibition of the sensitive parental clone. Unlike most 6-MP-resistant cell lines described previously, both neuroblastoma populations display normal activities of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) but greatly reduced accumulation of ¹⁴C-labeled 6-MP. Drug accumulation was inhibited by adenine, blocked by dinitrophenol but not ouabain and strongly temperature dependent, suggesting a need for cytoplasmic phosphoribosylation. Possible mechanisms for this reduction in 6-MP retention are discussed. It is possible that the resistant cells possess a mutated form of HGPRT with an altered K_m for 6-MP which can thus distinguish 6-MP from its normal substrates, hypoxanthine or guanine, or that intracellular 5'-phosphoribosyl-1-pyrophosphate levels are deficient in the mutants. Importantly, eight clones isolated in 6-MP free media from the 110-fold resistant population of cells demonstrated quantitatively identical growth inhibition at all drug concentrations tested, suggesting that the original 110-fold resistant neuroblastoma population was homogenous with respect to its mechanisms of resistance. This homogeneity may make it possible to select a second drug which acts synergistically in suppressing resistance to 6-MP.

- 5358 REGULATION OF ORNITHINE DECARBOXYLASE IN 3T3 CELLS BY PUTRESCINE AND SPERMIDINE: INDIRECT EVIDENCE FOR TRANSLATIONAL CONTROL. (Eng.) Clark, J. L. (Coll. Medicine, Univ. California at Irvine, Irvine, Calif. 92664); Fuller, J. L. *Biochemistry* 14(20):4403-4409; 1975.

The effect of putrescine and spermidine on ornithine decarboxylase activity in cultures of 3T3 cells was investigated. Putrescine (10^{-4} M) or spermidine (10^{-5} M) prevented the increase in ornithine decarboxylase activity brought about by pituitary growth factors, and resulted in a rapid, specific, and reversible reduction of enzyme activity in cultures previously stimulated by the growth factors. These effects were not due to polyamine toxicity, and did not require other organic medium components. The amines apparently share a single carrier-mediated transport system in 3T3 cells. Methylglyoxal bis(guanylhydrazine) (10μ M), an inhibitor of spermidine synthesis from putrescine, was found to also inhibit uptake of each amine. Each amine was effective without further metabolism. Since ornithine decarboxylase activity decayed more

rapidly in the presence of each polyamine than after addition of camptothecin (20 $\mu\text{g/ml}$), the major locus of amine action appears to be in the cytoplasm. However direct inhibition of the enzyme *in vivo* by assimilated amines appeared to account for at most a small part of the reduction in activity, a conclusion supported by the inability to recover activity *in vitro*. Also, neither amine seemed to act by accelerating enzyme inactivation. When amines were removed from the medium, the subsequent recovery of enzyme activity was totally prevented by trichodermin (5 $\mu\text{g/ml}$), an inhibitor of protein synthesis, but was only slightly reduced by camptothecin (20 $\mu\text{g/ml}$). It is suggested that both putrescine and spermidine reduce ornithine decarboxylase activity by selectively inhibiting translation.

5359 STUDIES ON THE KINETICS OF GLYCOSIDASES FROM CHEMICALLY-INDUCED RAT COLONIC TUMOURS AND NORMAL RAT COLON. (Eng.) Mian, N. (Sch. Med., Univ. Leeds, England); Herries, D. G.; Cowen, D. M.; Batte, E. A. *Biochim. Biophys. Acta* 391(1):179-188; 1975.

Studies were carried out to compare the kinetics of glycosidases of tumors and of the colonic mucosa in order to assess the enzyme increase in the neoplastic transformation. K_m values of β -*N*-acetylglucosaminidase, β -*N*-acetylgalactosaminidase, β -galactosidase, and α -L-fucosidase of distal colonic tumors, induced in Wistar rats by 1,2-dimethylhydrazine (20 mg/kg, sc, once weekly for 18-22 wk), were found to be significantly different compared with the values for the enzymes of the colonic mucosa of the control and tumor-bearing animals and of the proximal colonic tumors. The inhibition kinetics data also showed a significant difference between the enzymes of the distal colon tumors and of other experimental tissues. The data on the effect of pH on enzyme kinetics (pK values) showed no significant difference in the catalytic groups of the active centers of enzymes from tumors and from the control colonic mucosa. Tumor β -*N*-acetylglucosaminidase and β -*N*-acetylgalactosaminidase compared with the enzymes from other experimental tissues were found to be different in their thermal inactivation kinetics. K_m values of 14 day old fetal intestinal β -*N*-acetylglucosaminidase and β -*N*-acetylgalactosaminidase were significantly different from the values obtained for the adult mucosal enzymes but were similar to those of the distal colonic tumor enzymes.

5360 THE EFFECT OF SH-BLOCKING AGENTS ON THE *p*-NITROPHENYLPHOSPHATASE ACTIVITY OF INTACT EHRlich ASCITES TUMOR CELLS. (Eng.) Löffler, M. (Physiologische-chemisches Institut der Universität Marburg, Marburg/Lahn, West Germany); Schneider, F. *FEBS Lett.* 56(1):66-69; 1975.

p-Nitrophenylphosphatase (pNPPase) activity was investigated in untreated intact Ehrlich ascites tumor cells from NMRI mice and in cells with surface modifications induced by neuraminidase and (SH)-blocking agents. Incubation of intact tumor cells with *p*-nitrophenylphosphate (pNPP) resulted in a

linear time-dependent liberation of *p*-nitrophenol. Hydrolysis of pNPP appeared to be initiated by enzyme localized in the plasma membrane of the intact cells. In accordance with a previous suggestion that pNPPase activity is part of the (Na⁺-K⁺)-stimulated ATPase of the outer membrane, a 75% activation of the enzyme occurred on incubation of cells with 1.2 mM pNPP and the same concentration of ATP. Neuraminidase removed neuraminic acid from the cell surface and this removal was accompanied by enhanced pNPPase activity. Sterical factors and the state of charge of the inhibitor seemed to be important for the degree of enzyme inhibition by SH-blocking agents at 10^{-4} M. The inhibition ranged from 25% with iodoacetic acid to 75% and 78%, respectively, with *p*-chloromercuribenzoic acid and *p*-chloromercuribenzenesulfonic acid. No correlation could be detected between the effect of the blocking agents on pNPPase activity and their effect on intracellular nonprotein SH levels (the acid-soluble thiol content of cells). At 0.08 mM, the two mercurial compounds had no influence on nonprotein SH or the number of surface SH groups although they were the strongest enzyme inhibitors.

5361 PYRUVATE KINASE ISOZYME PATTERNS OF HUMAN NEOPLASTIC, FETAL AND ADULT TISSUES.

(Eng.) Kamel, R. (Institut für Anthropologie und Human genetik der Universität, D-800 München 2, Richard Wagner-Strasse 10¹, West Germany); Schwarzfischer, F. *Humangenetik* 28(1):65-69; 1975.

Pyruvate kinase isozyme patterns in 53 diverse human tumors were compared with those of normal adult and fetal organs as part of a study to find typical "malignancy-isozyme" patterns which can be attributed to human cancer in general. The following primary human tumors were tested: glioblastomas (6), astrocytomas (3), meningiomas (4), melanoblastomas (4), lung- (7), stomach- (8), kidney- (11), rectal- (4), colonic- (2), sigmoid- (1), cecum- (1), and skin (2) carcinomas. Six fetuses between the 2nd and 7th mo of gestation were examined and the following organs tested: brain, lung, heart, stomach, kidney, liver, and skeletal muscle. Tissue homogenates were centrifuged at 30,000 $\times g$ for 25 min at 4 C and 5 μl from each supernatant was applied to filter papers for horizontal starch gel electrophoresis. Incubation lasted from 30 min to 3 hr at 37 C. Normal adult human pyruvate kinase was resolved into four isozymes. Fetal brain and liver each showed a unique isozyme band that was not seen in any other specimen. In all normal adult organs, one of the isozymes (designated PK IV) predominated; in all tested tumors, except in the rather benign meningiomas, another isozyme (designated PK I) predominated. The strongest PK I bands appeared in highly malignant kidney carcinomas and in melanoblastomas; they developed after 30 min of gel incubation, while the PK IV bands in normal tissues could only be detected after 3 hr. All fetal organs showed PK IV in varying intensities; in addition, a strong PK band appeared in all fetal organs including placenta, but not in the brain. The appearance of PK I in most fetal organs indicates that it is required in rapidly growing, not highly differentiated and strongly glycolyzing tissue in general.

It is suggested that PK I is the more convenient isozyme for cancer cells because it is always in an active form, has a lower K_m value for phosphoenolpyruvate, and is not inhibited by excess ADP.

- 5362 THE SEPARATION OF TWO FORMS OF URIDINE KINASE FROM THE NOVIKOFF HEPATOMA. (Eng.) Keefer, R. C. (Ohio State Univ., Coll. Medicine, Columbus, Ohio 43210); McNamara, D. J.; Webb, T. E. *Cancer Biochem. Biophys.* 1(2):107-110; 1975.

Two forms (isozymes) of uridine kinase were demonstrated in the 30-50% ammonium sulfate fraction of the cytosol from Novikoff ascites hepatoma. The uridine kinase was partially purified from the cytosol using streptomycin sulfate and ammonium sulfate fractionation. The 30-50% ammonium sulfate fraction was dialyzed twice for three hours against 50 mM Tris buffer pH 7.4, containing 20% glycerol and 20 mM mercaptoethanol. The relative mobilities of the two species to the anode in a 4.5% gel were the reverse of their relative orders of elution from a Sepharose 6B or DEAE-cellulose column. It is concluded that the two uridine kinase isozymes present in the Novikoff hepatoma ascites cells differ in size and net charge.

- 5363 HYDROXYLATION OF TESTOSTERONE AT CARBONS 1, 2, 6, 7, 15 AND 16 BY THE HEPATIC MICROSOMAL FRACTION FROM ADULT FEMALE C57BL/6J MICE. (Eng.) Ford, H. C. (Harvard Medical Sch., 45 Shattuck St., Boston, Mass. 02115); Wheeler, R.; Engel, L. L. *Eur. J. Biochem.* 57(1):9-14; 1975.

The metabolism of a mixture of $[4-^{14}C]$ - and $[7\beta-^3H]$ testosterone by the hepatic microsomal fraction from adult female C57BL/6J mice was investigated. The following metabolites were identified by their mass spectra and by their retention times on gas chromatography on one or two phases: 1β -, 2β -, 6α -, 6β -, 7α -, 15α -, 15β -, 16α -, and 16β -hydroxytestosterone; 6α -, 6β - and 7α -hydroxy-4-androstene-3,17-dione; and 4-androstene-3,17-dione. A compound tentatively identified as 6- or 7-oxotestosterone was also isolated. 17β -Hydroxy-4,6-androstadien-3-one, 17β -hydroxy-1,4-androstadien-3-one, and 4,6-androstadiene-3,17-dione were identified but are considered to arise nonenzymatically from 7α -hydroxytestosterone, 1β -hydroxytestosterone and 7α -hydroxy-4-androstene-3,17-dione, respectively. The diversity in position of hydroxylation of testosterone exhibited by mouse liver microsomes, the presence of relatively high levels of hydroxylase activity, and the apparent absence or low level of 4-ene-reductase all indicate the value of using this animal for studies of the genetic regulation of the activity, inducibility, and stereospecificity of these enzyme systems.

- 5364 CIRCULATING LEVELS OF PROLACTIN IN HUMAN BREAST CANCER. (Eng.) Sheth, N. A. (Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012 India); Ranadive, K. J.; Suraiya, J. N.; Sheth, A. R. *Br. J. Cancer* 32(2):160-167; 1975.

Serum prolactin concentrations were measured by radioimmunoassays in 98 patients with cystic mastitis, and ten patients with gynecomastia and compared with that of age-matched normal women. Blood samples were collected from the subjects in the afternoon between 1 and 4 pm. The serum prolactin levels in the patients with breast cancer, gynecomastia or cystic mastitis were similar to that in normal women. The levels of prolactin in the luteal phase of the cycle were higher than that in the early follicular phase in normal women. Prolactin may be involved in the maintenance, if not initiation, of some human breast cancers. The fact that some success was achieved in regression of breast cancer by treatment with agents like CB-154 and L-DOPA, which inhibit prolactin secretion, implicates the role of prolactin (acting alone or synergistically with other hormones) in the etiology of breast cancer.

- 5365 OESTROGEN RECEPTORS IN BREAST CANCER: A CHANGING CONCEPT. (Eng.) Leclercq, G. (Dept. Medicine, Institut Jules Bordet, Centre des Tumeurs de l'Universite Libre de Bruxelles, 1000 Brussels, Belgium); Heuson, J. C.; Deboel, M. C.; Matthei, W. H. *Br. Med. J.* 1(5951):185-189; 1975.

Estrogen receptors in 214 primary breast cancers and 168 metastatic deposits were assayed by measuring the binding affinity of their cytosol fraction for 3H -estradiol- 17β at 18 C. Receptors were found in 156 (73%) of the primary tumors and in 98 (58%) of the metastatic tumors. When the findings were considered chronologically, these proportions reached 82% and 70%, respectively, in the second half of the study as against 64% and 46% in the first half. Receptors were not found in samples of normal breast tissue, but small amounts were present in tissue from some hyperplastic lesions and in male gynecomastia. Receptor concentrations in the malignant samples were evenly distributed over a wide range of values, suggesting that even "negative" tumors might contain trace amounts undetectable by the method used. Each tumor was characterized by a given level of receptor concentration. In most cases, the amounts found in the invaded axillary nodes and their corresponding primary tumors were the same. Quantitative measurement of receptor content might assess the degree of hormone dependence of a tumor. It is therefore suggested that quantitative rather than qualitative assessment should provide an appropriate criterion for studies of biochemical and clinical correlations.

- 5366 HIGH MOLECULAR WEIGHT FORMS OF ADRENOCORTICOTROPIC HORMONE IN THE MOUSE PITUITARY AND IN A MOUSE PITUITARY TUMOR CELL LINE. (Eng.) Eipper, B. A. (Dept. Chemistry, Univ. Oregon, Eugene, Oreg. 97403); Mains, R. E. *Biochemistry* 14(17):3836-3844; 1975.

Denaturing solvents were used to determine the molecular weight of the ACTH activity in mouse pituitary, in an ACTH secreting mouse pituitary tumor cell line (AtT-20/D-16v), and in the tissue

culture medium from the pituitary tumor cells. ACTH activity was quantitated by radioimmunoassay and by bioassay. It was possible to utilize guanidine hydrochloride or sodium dodecyl sulfate in characterizing the multiple forms of ACTH because treatment of porcine ACTH (the 39 amino acid polypeptide form of ACTH, $\alpha(1-39)$), pituitary extracts, tumor cell extracts, and tumor cell tissue culture medium with these denaturants did not diminish the immunological ACTH activity. Based on gel filtration in the presence of guanidine hydrochloride, extracts of the pituitary tumor cells and the mouse pituitary were found to contain three distinct molecular weight classes of ACTH activity. The major form of ACTH had a molecular weight similar to $\alpha(1-39)$ (molecular weight 4,000-5,500), but there were significant amounts of two higher molecular weight forms of ACTH: molecular weight 6,500-9,000 and molecular weight 20,000-30,000. The 6,500-9,000 molecular weight form of ACTH was the major form of ACTH in the tissue culture medium; there was no peak of $\alpha(1-39)$ size ACTH in the medium. In the radioimmunoassay, all three forms of ACTH generated competitive binding curves parallel to that of porcine $\alpha(1-39)$; in the bioassay (stimulation of steroidogenesis in a mouse adrenal tumor cell line) the dose response curve for each of the molecular forms of ACTH was parallel to that for porcine $\alpha(1-39)$. The AtT-20/D-16v cell line provides a convenient source of material for studies of the molecular nature of the high molecular weight forms of ACTH.

- 5367 LOW-FIBER INTAKE AS AN ETIOLOGIC FACTOR IN CANCER OF THE COLON. (Eng.) Modan, B. (Chaim Sheba Med. Cent., Tel Hashomer Israel); Barell, V.; Lubin, F.; Modan, M.; Greenberg, R. A.; Graham, S.; *J. Natl. Cancer Inst.* 55(1):15-18; 1975.

A case-control dietary study of 198 patients with cancer of the colon and two matched control groups demonstrated a significantly lower fiber consumption frequency among the cancer patients. This difference was not confined to a few items. Of the 73 items on the fiber list, 61 were eaten less often by the cancer patient than by a neighborhood control, and 57 were consumed less frequently than by a surgical control. The patients' origins were: 87% European born, 8% Asian and African born; 60% came to Israel before 1950. The controls were matched to cases for sex, age, origin, and time of residence in Israel. The last three factors together are closely associated with socioeconomic level in Israel. These findings support the hypothesis that low-residue foods play an etiologic role in colon carcinogenesis. A mechanism related to the possible potential carcinogenic properties of degraded biliary compounds may be implicated.

- 5368 CONTRIBUTION TO THE PROBLEM OF THE WEAK A-BLOOD GROUPS. (Eng.) Sachs, V. (Fac. Med., Univ. Kiel, West Germany); Friedburg, S.; Finke, M.; Szirmai, E. *J. Inst. Nucl. Eng.* 16(3):79-81; 1975.

The problem of assigning a variant weak A blood group to one of the known A forms in the proposita's family is discussed. Based on serologic criteria, it is suggested that weak blood group A types except the types A_1 , A_2 , A_3 and A_{int} belong to two main groups A_x and A_m defined by the agglutination and absorption properties by the ABO-antibody specificities in the serum and by the secretor status. A third group, well defined by action of the suppressor gene system $H-h$, is the 'Bombay-type' (O_h^A). It is doubtful whether the leukemia associated weak A-forms are a further separate group. They belong also to the second group A_m . The knowledge of these weak A blood groups is important for clinical medicine and also for radiation (nuclear) hematology, with respect to the compatible transfusion as well as to the forensic blood group serology with respect to the correct paternity conclusion and to the paternity presumption by means of statistical methods.

- 5369 AUTOMATED CYTOFLUOREMETRY OF SOLID MALIGNANT TUMORS AFTER CELL DISPERSAL BY MEANS OF INTRAPERITONEAL CULTIVATION OF CELL COMPLEXES IN YOUNG RATS. (Ger.) Stöhr, M. (Deutsches Krebsforschungszentrum Heidelberg, Institut für Experimentelle Pathologie, D-6900 Heidelberg, Im Neuenheimer Feld 280, West Germany); Löhrke, H.; Sandbrink, H. *Beitr. Pathol.* 155(1):36-43; 1975.

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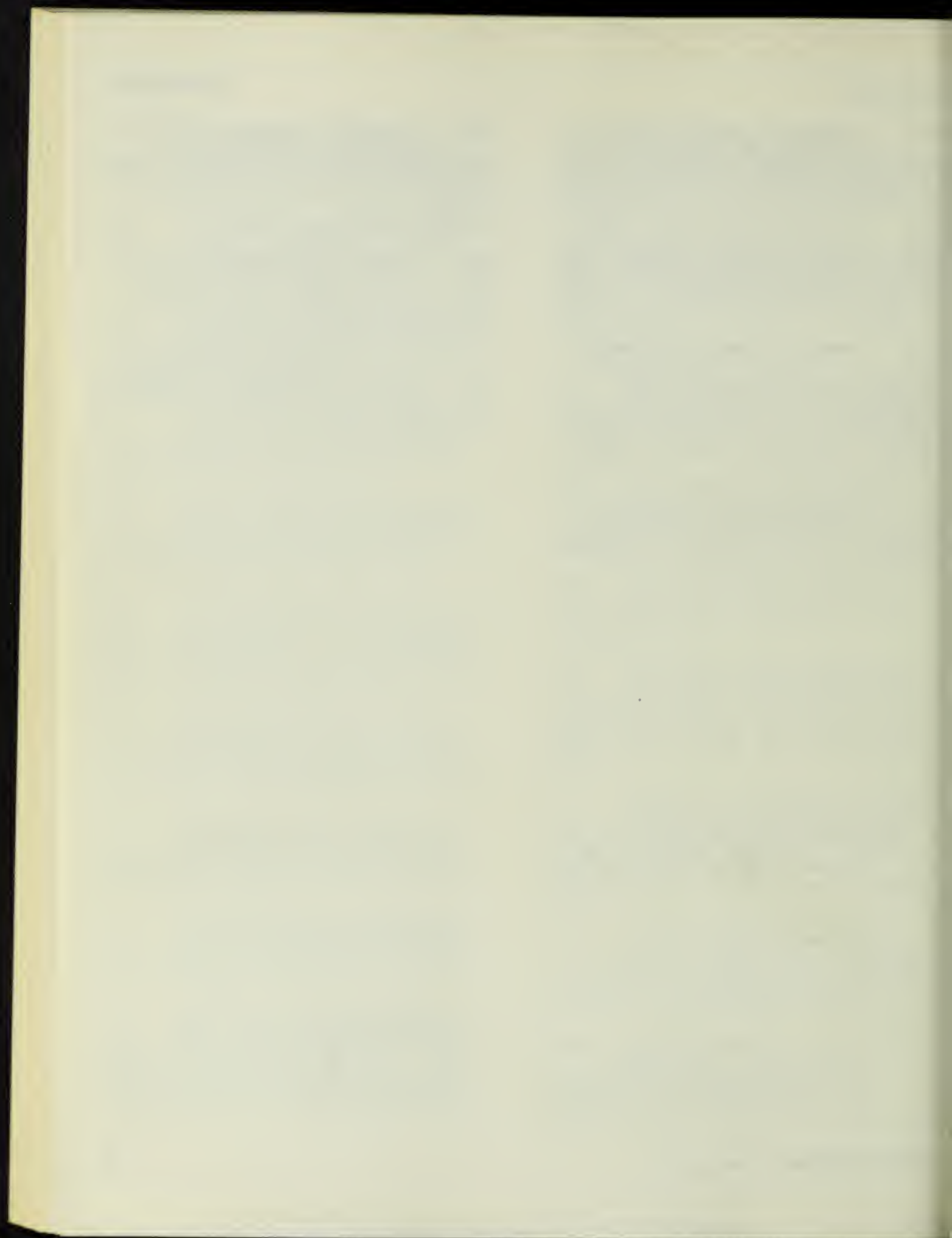
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BENNINGHOFF, D.L. 5172*	BLOUGH, H.A. 4835*	BROYN, T. 5189
BENTLEY, P. 4937*	BODDIE, A.W., JR. 5111	BRUCE, A.W. 5259*
BENVENUTI, C. 5180*	BODURTHA, A.J. 5100	BRYAN, G.T. 4909*
BERCHTOLD, H. 5199	BOERYD, B. 4871	BUCHLER, D.A. 5198
BERDINSKIKH, N.K. 5388*	BOEYRD, B. 5090	BUCKEL, U. 4974*
BERG, P. 5038, 5041, 5042	BOIRON, M. 5056*, 5099	BUCOVAZ, E.T. 4938*
BERGSTRESSER, P.R. 5291*	BOLDT, I. 5263*	BULDAKOV, L.A. 4996*
BERKVENS, J.M. 5088	BOLOGNESI, D.P. 5061*	BURCHENAL, J.H. 5207
BERLIN, R.D. 4836*	BONA, C. 5117, 5169*	BURGER, P.C. 5048*
BERNARD, C. 5099	BONE, E. 5191	BURGIO, G.R. 5089
BERNARD, J. 5242*	BONMASSAR, A. 5394*	BURK, M.W. 5079
BERNFIELD, M.R. 5036	BONMASSAR, E. 5394*	BURK, R.L. 5260*
BERNSTEIN, I.D. 5162*	BOONE, C.W. 5130*	BURROWS, D. 5255*
BEVAN, M.J. 5105	BOSCHETTI, N.V. 5273*	BURTIN, P. 5143*
BEY, E. 5377*	BOSE, S.K. 5024	BUSBY, W.F. 4930*
BHARGAVA, A. 5109	BOTELLI, A.M. 5089	BUSCH, R.H. 4900
BIASI, G. 5167*	BOURNE, K.C. 5071	BUSELMAIER, W. 4983*
BIBBO, M. 4873	BOUSSER, J. 5239*	BUTEL, J.S. 5037
BIBILASHVILI, R.SH. 5393*	BOUTWELL, R.K. 4869	BUTLER, T.P. 5197
BIEDLER, J.L. 4811, 5245*	BOWEN, J.M. 5328	BYERS, V.S. 5159*
RIESSMANN, H. 4899	BRADSHAW, R.A. 4816	CADIOU, M. 5239*
BIGLEY, R. 5019	BRANKOW, D.W. 4939*	CAIRNS, J. 4850*
BIGNAMI, M. 4954*	BRANNEN, G.E. 5108, 5110	CALAFAT, J. 5176*
BIGNER, D.D. 5046*, 5047*, 5048*	BRENNKUS, L.M. 5301*	CALVIN, M. 4801
BILEK, O. 5069	BRIDGES, B.A. 4856	CAMERON, D.G. 5297*
BINKERT, F. 4984*	BRISCOE, W.T. 5328	CAMMOUN, N. 5013
BIRNIE, G.D. 5020	BRODER, S. 5087	CAMPOS, G.M. 5249*
BLACKMAN, M. 5087	BRODESTSKY, A.M. 5163*	CAMUS, M. 4953*
BLANK, K.J. 5060*	BRODEUR, G.M. 5309	CANNON, G.B. 5171*
BLASECKI, J.W. 5080	BROOKES, P. 4856, 4879	CAPDEVILA, J. 4883, 5304
BLAT, C. 5312	BROOKS, R.F. 5337	CARBON, J. 5038, 5042
BLICHSTEIN, S. 4907*	BROSMAN, S. 5070	CARCASSONNE, Y. 5144*
BLOCK, M.B. 5201	BROSSARD, M. 5220*	CARDAMONE, G. 4954*
BLUMENDAL, H. 5332	BROUET, J.C. 5241*	CARDOSO, E.A. 5052*

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CARERE, A. 4954*	CHUANG, L.F. 5353	CRANMER, M.F. 4849*
CARIELLO, L. 4857	CHUANG, R.Y. 5353	CREAGHE, E. 5168*
CARLMARK, B. 5238*	CHUAT, J.C. 5099	CRESCENZI, V. 4857
CARLSON, R.P. 4882	CIACCIO, E.I. 4882	CREUTZFELDT, W. 5193
CARNEY, J.A. 5261*	CLARK, J.L. 5358	CRISWELL, S.S. 5114
CARTER, R.L. 4826*	CLEMENCON, G. 5230*	CROCE, C.M. 5033
CASANOVA, P. 5267*	CLETON, F.J. 5176*	CROSBY, E.H. 4992*
CASSADY, J.R. 5292*	CLOYD, M.W. 5048*	CUDKOWICZ, G. 5067
CASSANI, G. 4982*	COATES, H.L.C. 5248*	CULLEN, K.J. 5104
CASSIMAN, J.J. 5036	COETZEE, M.L. 5343	CZEIZEL, A. 4932*, 4976*
CASTO, B. 4906*, 4942*	COFFEY, D.S. 5108	DALTON, A.J. 5004
CATINI, F. 5180*	COHEN, E.P. 5095	DAMBAYANT, C. 5154*
CAUCHI, M.N. 5346	COHN, M. 5082	DAMJANOV, I. 5264*
CAUCHY, L. 5016	COLCHER, D.M. 5065*	D'ANGIO, G. 5237
CESARINI, J.-P. 5085	COLIZZA, S. 5180*	DANIEL, M.T. 5241*
CHANG-LO, M. 5204	COLLARD, A. 5066	DANIEL, M.-T. 5242*
CHANY, E. 5143*	COLLAVO, D. 5167*	DANIELE, R.P. 5147*
CHAPMAN, R.S. 5184	COLNAGHI, M.I. 5026	DARDANO, J. 5114
CHARKVIANI, L.I. 5279	COLOMBATTI, A. 5167*	DATTA, S.K. 5120
CHAUVERGNE, M.J. 5370*	COLOMBIES, P. 5244*	DATTWYLER, R.J. 5113
CHAUZY, C. 5220*	CONTI, G. 4954*	DAU, P.C. 5384*
CHEDID, L. 5169*	COOGAN, P.S. 5195	DAVID, C.S. 5155*
CHEE, D.O. 5100	COOPER, H.K. 4890, 4894	DAVIDSON, N. 5009
CHIBBER, B.A. 5310	CORBERAND, J. 5236*, 5244*, 5253*	DAVIDSON, N.E. 4930*
CHIRIGOS, M.A. 5101	CORNET, E. 5258*	DAVIS, W.C. 5093
CHISAKA, N. 4917*	COTTER, S. 5150*	DAWSON, P.J. 5059*
CHIU, C.W. 4909*	COTTLER-FOX, M. 5045*	DAY, N.E. 5299*
CHIU, J.-F. 5352	COUDERT, F. 5016	DE CARLI, L. 4982*
CHO, B.R. 5093	COURTNEY, R.M. 5250*	DE LAJARTRE, A.Y. 5258*
CHO, H.Y. 5054*	COUSINS, R.J. 4997*	DE RIDDER, L. 5217
CHO, J.-R. 5005	COWEN, D.M. 5359	DE SERRES, F.J. 4904*
CHRISTOV, K. 5338	CRADDOCK, C. 5352	DE-THE, G. 5013
CHU, B.C.F. 4889	CRAIG, A.W. 4893	DEAN, B. 4856
CHU, T.M. 5109, 5160*	CRAIG, D.K. 4900	DEAN, J.H. 5171*

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DEBOEL, M.C. 5365	DOUGLASS, H.O. 5228*	EROKHIN, V.N. 5307
DECLEVE, A. 5023	DRAKE, S. 4999	ESSEX, M. 5150*
DEGROOT, L.J. 5102	DRASAR, B.S. 4931*, 5191	EVANS, H.J. 4896
DEIGERT, F.A. 4842*	DREOSTI, I.E. 4886	EVANS, L.H. 5019
DEKNUDT, G. 4933*	DRESLER, S.L. 5059*	EVEGE, E. 5152*
DEL MONTE, U. 4821	DROBNJAK, P. 5264*	EXELBY, P. 5207
DEMPO, K. 4917*	DROCHMANS, P. 5303	FABBRIS, R. 5167*
DENK, H. 5269*	DULLMANN, J. 5243*	FAHL, W.E. 4875
DEPAMPHILIS, M.L. 5041	DUNBAR, J.A. 5224*	FAHMY, M.J. 4891
DERMER, G.B. 5391*	DUNCAN, J.R. 4886	FAHMY, O.G. 4891
DESAI, L.S. 5330	DUNN, C.Y. 5008	FAILLE, A. 5064*
DESAI, P.R. 5161*	DURM, M. 5087	FALCK, B. 5318
DESANTO, L.W. 5248*	DUTAU, G. 5236*, 5253*	FARACI, R.P. 5181
DESGRANGES, C. 5013	DUTTON, A.C. 5385*	FARMAN, A.G. 5262*
DESMET, V.J. 4853	EBEL, R.E. 5348	FAVRE, R. 5144*
DEVINE, K.D. 5248*	EDMAN, C.D. 5268*	FEDOROV, N.A. 4820
DI GIUSEPPE, G. 4954*	EGAWA, K. 5126*, 5146*	FEIGL, W. 5269*
DI LERNIA, R. 4982*	EHRHARDT, J.P. 5300*	FELDMAN, M.E. 5151*
DI MARCO, A. 4857	EIPPER, B.A. 5366	FELTKAMP, C.A. 5175*
DI MARCO, A.T. 5166*	EKBAL, S. 5195	FERRONE, S. 5177*
DI PAOLA, M. 5187*	ELIAS, E.G. 5228*	FEUILLETTE, A. 5052*
DIDOLKAR, M.S. 5228*	ELICEIRI, G.L. 5387*	FIELDSTEEL, A.H. 5059*
DIEFICH, M.P. 5177*	ELIOPOULOS, G. 5237*	FINKE, M. 5368
DIPAULO, J. 4906*, 4942*	ELIZAN, T.S. 5153*	FIORETTI, M.C. 5394*
DIPPLE, A. 4828*	ELKIND, M.M. 4990	FIRMINGER, F.I. 4908*
DJELINEQ, A. 4981*	ELLOUZ, R. 5013	FISCHER, C.D., JR. 4863
DMOCHOWSKI, L. 4810	EMANUEL, N.M. 5307	FISCHER, R. 4809
DOERFLER, W. 5002	EMMELOT, P. 5175*	FISCHER, S. 4870
DOFUKU, R. 5245*	ENGEL, L.L. 5363	FISCHINGER, P.J. 5021
DOI, H. 4955*, 4957*	ENGELER, V. 5199	FISH, S.A. 4938*
DOLL, R. 4829*, 4848*	ENGELHARDT, G. 4972*	FISHBEIN, A.V. 4995*
DOMENICONI, R. 5231*	ENOMOTO, M. 4915*, 4923*, 4924*	FJELDE, A. 5152*
DORF, M.E. 5156*	ENOMOTO, Y. 5115	FLAKS, B. 4860

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FLANDRIN, G. 5241*, 5242*	FURUKAWA, K. 5136*	GOLDFEDER, A. 5376*
FLEIG, J. 4983*	FUSENIG, N.E. 5305	GOLDIN, A. 5394*
FOCAN, C. 5178*	GAD, A. 5221*	GOLDMAN, C. 5087
FOGH, J. 5143*	GAFFNEY, P.R. 5121	GOLDMAN, E. 5327
FOLEY, G.E. 5330	GALLO, R.C. 4833*, 5006, 5044	GOLDSCHMIDT, B.M. 4861
FORBES, P.D. 4991	GANGADHARAN, P. 5282	GOLDSTEIN, L.T. 5074
FORGD, H.C. 5363	GANGAL, S.G. 5381	GOLDSTEIN, M.N. 5339
FOREST, M. 5251*	GANTT, R. 5049*	GOMOLKA, D.M. 5108
FORGHANI, B. 5098	GARDNER, M.B. 5007	GOODHEART, C. 4942*
FORMAN, J. 5112	GARMAISE, A.B.-K. 5149*	GOTHO, M. 4921*
FOX, A.J. 5294*	GAYLOR, J.L. 5397*	GOULIAN, M. 5339
FOX, M. 4950*	GAZDAR, A.F. 5025	GOUST, J.M. 5066
FOX, R.M. 5339	GEBHART, E. 4951*, 4979*, 4980*	GRAEVS'KAA, N.A. 5393*
FRAENKEL-CONRAT, H. 4952*	GELBOIN, H.V. 4883	GRAHAM, S. 5367
FRAUX, J.L. 4865	GEORGOPOULOS, S.G. 4946*	GRANTHAM, F.H. 5197
FRAZIER, W.A. 4816	GERMAIN, R.N. 5156*	GRAPPELLI, C. 5062*
FREEMAN, A.E. 4884	GERNER, R.E. 5336	GRAYKOWSKI, E.A. 5181
FRIDMAN, W.H. 5085	GETZ, M.J. 5020	GREENBERG, R.A. 5367
FRIEDEBURG, S. 5368	GHOSH, S.N. 5322	GREENBERGER, J.S. 5022
FRIEDRICH, E.G., JR. 5222*	GIELKENS, L.J. 5332	GREENE, M. 5086
FRIEND, C. 5064*	GILBERT, J. 4803	GRIFFIN, A.C. 5328
FRITZ, R.R. 5119	GILL, W. 4873	GRIZELJ, V. 5264*
FRYER, J.E. 4938*	GILLESPIE, D. 4833*, 5044	GRODZICKER, T. 5000
FUJII, H. 5214	GILLIAVOD, N. 4933*	GRONER, Y. 5326
FUJIMOTO, S. 5086	GILLIES, N.E. 4988	GROSS, M.A. 5382*
FUJIMURA, S. 4967*, 5349	GINGELL, R. 4862	GROUDINE, M. 5030
FUJITA, M. 4964*, 5132*	GIRARDET, R.E. 5172*	GROZDEA, J. 5244*
FUJITANI, H. 4858	GLEBOVA, M.J. 5280	GRUBER, J. 5050*
FUJIWARA, H. 5131*	GLICK, J.L. 5385*	GRUNBERGER, D. 4907*, 5395*
FUKUDA, T. 4962*	GOCHO, Y. 5133*, 5135*	GRUNFELD, K. 5293*
FUKUSHIMA, S. 4922*, 4959*	GOERTTLER, K. 4854	GRUSZKA, S. 5223*
FUKUSHIMA, T. 4967*	GOH, K. 4989	GULLINO, P.M. 5197
FULLER, J.L. 5358	GOLDE, D.W. 5064*	GUNNARSSON, A. 5079

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GUPTA, S. 5298*	HASS, G.M. 5195	HIPAYAMA, T. 5281
GVAMICHAHA, D.A. 5279	HASSOUN, J. 5216	HIRONO, I. 4925*
HABER, B. 5380*	HATCH, G. 4942*	HIROTA, T. 4969*
HABU, S. 5115	HATGI, J.N. 5050*	HNILICA, L.S. 5352
HADIDI, A. 5055*	HATTORI, T. 5141*	HOCHACHKA, B.C. 4874
HAGEMAN, P.C. 5176*	HAUSMAN, M. 5070	HOFFMANN, D. 4901
HAGER, H. 5215	HAUSMANN, K. 5243*	HOFMAN-BANG, A. 4967*
HAGMAR, B. 4871	HAVERMAN, J. 5176*	HOGUE-ANGELETTI, R.A. 4816
HAINES, H.G. 5382*	HAY, D. 5092	HOLFORD, R.M. 4994*
HAIZUKA, S. 4965*, 5187	HAYASHI, O. 4924*	HOLLENBERG, M.D. 5373*
HAKIM, A.A. 5072	HECHT, S.S. 4901	HOLLINSHEAD, A.C. 5107
HAKOMORI, S. 4819	HEHLMANN, R. 5005	HOLMES, E.C. 5111
HALL, T.L. 5047*	HEINE, U.I. 5045*	HOLOUBEK, V. 4858
HALLORAN, P. 5155*	HELIA, C. 5304	HOLST, J.J. 5232*
HALPRIN, K.M. 5291*	HELLSTROM, I. 5096	HOLYOKE, E.D. 5228*
HAMAOKA, T. 5131*, 5140*	HELLSTROM, K.E. 5096	HOLZNER, J.H. 5269*
HAMELIN, R. 5056*	HELPAP, B. 5263*	HOOD, C. 5092
HAMMERSLEY, P.A.G. 5346	HEMPER, K. 5324	HORWITZ, O. 5293*
HANAICHI, T. 5127*	HEMSELL, D.L. 5268*	HOSHI, K. 4955*, 4957*
HANANUCHI, M. 4959*	HERBERMAN, R.B. 5171*	HOSHINO, K. 5209
HANSMANN, I. 4822*	HEROS, M. 5300*	HOSHINO, M. 5142*
HARA, K. 4970*, 5347	HERRIES, D.G. 5359	HOUCHEHS, D. 5394*
HARA, S. 5140*	HERWIG, A. 4975*	HOYE, K. 5102
HARADA, M. 4923*	HEUER, R. 5330	HRABOWSKA, M. 5196
HARADA, Y. 4918*	HEUSON, J.C. 5365	HSIUNG, G.D. 4998
HARBACH, P.R. 5047*	HIBINO, T. 4959*, 4970*	HUBERMAN, E. 4902
HARDY, W.D., JR. 5150*	HIGUCHI, K. 4884	HUDSON, J.L. 5151*
HAREL, L. 5312	HIKOSAKA, Y. 4959*	HUEBNER, R.J. 5054*
HARFIS, H. 4890	HILDES, J.A. 5297*	HUGHES, E.S.R. 5190
HARRIS, J.E. 4837*	HILGERS, J. 5175*, 5176*	HULL, S.F. 5201
HARRIS, M.A. 5354	HILL, M.J. 4931*, 5191	HUMPHREY, R. 5087
HARTWICH, G. 4951*	HINE, J. 4863	HUMPHREY, W., JR. 5075
HARVEY, S.R. 5160*	HIRAIDE, H. 4955*, 4957*	HUNTER, G.W. 5266*
HASHIMOTO, Y. 5125*	HIRAO, K. 4922*, 4927*	HURWITZ, J. 5326

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HUTCHISON, G.B. 4845*	JAFFEE, N. 5292*	KAMLAG, D. 5175*
HUTCHISON, H.T. 5380*	JAKOBSSON, S.W. 5304	KAMMEN, H.C. 4864
IAMPOL'SKAIA, S.A. 4995*	JANOSKO, N. 4936*	KAMOGAWA, A. 4923*
ICHIDA, F. 5106	JANSSSEN, A.P.M. 5332	KANAHARA, H. 5186
ICHINOE, M. 4924*	JARRETT, O. 5092	KANAYA, T. 5128*
IDEI, S. 4957*	JARRETT, W. 5092	KANAZAWA, K. 4926*
IGARASHI, Y. 5317	JARVIS, B. 4825*	KANEKO, A. 4917*
ILEA, E. 4903	JASMIN, C. 5018	KANEMATSU, T. 4916*
ILLMENSEE, K. 5210	JEEJEEBHoy, H.F. 4807	KANG, Y.H. 4876
IMAI, M. 5142*	JEMEC, B. 5229*	KANZAKI, M. 4971*
IMAMURA, A. 4897	JERNSTROM, B. 4883	KAPLAN, H.S. 5023
INABA, S. 5132*	JERNSTROME, B. 5304	KAPPAS, A. 4946*
INOKUCHI, K. 4966*, 4968*	JOHNSON, R.T. 5334	KARAKI, Y. 5186
INOUE, H. 4949*	JOHNSON, R.W. 5050*	KARIM, J. 4974*
INOUE, K. 4927*	JOHNSON, T.S. 5151*	KARLINSKII, V.M. 5235*
INUI, N. 4914*	JOHNSSON, G. 4871	KATO, K. 4925*
IOKI, Y. 4897	JONES, P. 5032	KATSUTA, H. 5123*
IRVIN, G.L., III 5151*	JORDAN, L. 4999	KATYAL, S.L. 5343
IRVINE, A.R. 5226*	JORES, S. 5238*	KAVSAN, V.M. 5393*
IRWIN, D. 5356	JOUNG, J.I. 5102	KAWABATA, H. 4927*
ISHIBASHI, F. 5128*, 5132*	JULIEN, J.-P. 5220*	KAWACHI, T. 4958*, 4969*
ISHIDA, N. 5134*	JULLIEN, M. 5312	KAWAMATA, J. 4928*
ISHII, Y. 5128*	JUSSAWALLA, D.J. 5282	KAY, C.M. 4910*
ISHIOKA, K. 5188	KABAT, D. 5019	KEARNEY, R. 5148*
ISONO, S. 5188	KADAI, R.G. 5201	KEEFER, R.C. 5362
ITO, I. 5129*	KAISERLING, E. 5206	KELLY, P.J. 5380*
ITO, M. 4920*	KAKUNAGA, T. 4898	KELLY, R.K. 5037
ITO, N. 4927*, 4970*	KALENGAYI, M.M.R. 4853	KENSLER, T.W. 4930*
ITZHAKI, R.F. 4890, 4894	KALIN, G. 5195	KERMANI-ARAB, V. 5093
IWAMATSU, M. 4966*	KALLISTRATOS, G. 4881	KERR, D.A. 5250*
IWAMOTO, H. 5285	KALOGEROPOULOS, J. 5237*	KESSOUS, A. 5244*
IZUMI, T. 4960*, 4961*	KAMANO, T. 4960*	KETTERER, B. 4851*, 4910*
JACK, G.D. 5084	KAMEL, R. 5361	KHANNA, N.N. 5298*

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KIDA, S. 5315	KOHRO, T. 5186	KRUGER, G.R.F. 4809
KIKUCHI, K. 5128*, 5132*	KOITABASHI, T. 4963*	KUBASOVA, T. 5247*
KIKURA, M. 4962*	KOJIMA, K. 5127*	KUBO, T. 4919*
KIM, E.B. 5054*	KOJIMA, S. 4957*	KUBO, Y. 5192
KIM, K.M. 4908*	KOK, I.P. 5393*	KUCEROVA, M. 4978*
KIMMEL, C.B. 5323	KOKUMAI, Y. 5077, 5078	KUDO, G. 4955*, 4957*
KIMOTO, T. 4913*	KOLAR, G.F. 4986*	KUDO, H. 5129*
KIMURA, G. 5028	KOLER, R.D. 5019	KUHN, J.-M. 5234*
KIMZEY, S.L. 5114	KONAGA, E. 5077, 5078	KUKUSHKIN, I.M. 4866
KING, D. 4874	KONDO, A. 5133*, 5135*	KUKUSHKINA, L.M. 4866
KING, H.W.S. 4879	KONDO, M. 4914*	KULCAR, Z. 5287
KING, M. 5143*	KONDO, S. 4960*	KULCZYCKI, A., JR. 4947*
KINOSHITA, N. 4919*	KONIC-CARNELUTTI, V. 5287	KUMAR, S. 5350
KIRALY, J. 4976*	KOPROWSKI, H. 5033	KUNG, H.-J. 5009
KIRK, D. 5200	KOSHIBA, H. 5128*, 5132*	KUNISADA, K. 5078
KIRKLAND, W.L. 4934*	KOSS, L.G. 4844*	KURATA, H. 4924*
KISELEV, O.I. 5398*	KOURI, R.E. 4884	KURIHARA, M. 4960*, 4961*
KITAGAWA, M. 5131*, 5140*	KOURILSKY, F.M. 5085	LABATE, C. 5231*
KITAME, F. 5134*	KOVAC, R. 5371*	LAFFARGUE, F. 5267*
KITAMURA, H. 5306	KOYAMA, R. 5133*	LAGERLOF, B. 5238*
KITRON, N. 5351	KOYAMA, Y. 4969*	LAIRD, F. 4884
KLEIN, G. 5013	KOZAKIEWICZ, J. 5183	LAIRD, H. 5092
KLEINSMITH, L.J. 5039	KOZIMA, S. 4955*	LAMON, E.W. 5083
KLEISBAUER, J.P. 5296*	KOZIOROWSKA, J. 5316	LANG, J.M. 5246*
KLOSE, B.-J. 5271*	KOZLOVSKII, O.M. 4987	LANGE, H.W. 5324
KNAAP, A.G.A.C. 4935*	KOZLOWSKI, H. 5196	LANGENBACH, R. 4862, 4885
KNOBLAUCH, M. 5194	KRAJINA, Z. 5287	LANGVAD, E. 5229*
KNOWLES, M.E. 4803	KRAMERS, P.G.N. 4935*	LANMAN, B.M. 4865
KNUDSON, A.G., JR. 4812	KRASNODEBSKI, J. 5276*	LAPIN, V. 5029
KNYROV, G.G. 4987	KRAUSE, M.O. 5039	LAPREVOTTE, I. 5099
KOCH, C. 5091	KREIDER, J.W. 5314	LARDY, H.A. 5348
KOCK, Y. 5238*	KREMERS, P. 5399*	LARGIADER, F. 5194
KODAMA, M. 5132*	KRISHNAN, E.C. 5185	LARSEN, C.J. 5056*

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LASKA, E.M. 4870	LIEBERMAN, R. 5075	MALDONADO, J.E. 5208
LASZLO, J. 5353	LIJINSKY, W. 4895	MALTONI, C. 5179*
LAUCIUS, M.J. 5100	LILLY, F. 5060*	MANGALA, P.B. 5185
LAUMONIER, R. 5220*	LIN, C.Y. 5345	MANIGAULT, P. 5392*
LAUSCH, R.N. 5010	LINSELL, C.A. 5277	MANNAGH, J. 5226*
LAVAL, P. 5296*	LIVERMAN, J.L. 4831*	MANSON, L.A. 5074
LAWLEY, P.D. 4889	LO, K.W. 5014	MARCIONI, A.F. 5089
LAZARUS, L.H. 5351	LOCKWOOD, C. 5385*	MARCUS, D.M. 5319
LEBEDEV, V.N. 5283	LOFFLER, M. 5360	MARCUS, S.L. 5051*
LECLERCQ, G. 5365	LOHRKE, H. 5369*	MAREEL, M. 5217
LEDINKO, N. 5003	LOMACHENKOV, V.D. 5389*	MARGISON, G.P. 4890, 4893
LEE, J.C. 4941*	LOMAX, N. 5055*	MARKARIAN, M.S. 5390*
LEE, L.-F. 4940*	LOMMATZSCH, P. 5225*	MARQUUDAS, N.G. 5381*
LEFFERT, H.L. 5315	LONDON, W.T. 5014	MARSHAK, M.I. 5040
LENNE, Y. 5258*	LONGHINO, N. 5264*	MARTELL, E.A. 4806
LENNERT, K. 5013, 5206	LOPES, R.A. 5249*	MARTIN, G.M. 5336
LENNETTE, E.H. 5098	LU, Y.S. 5093	MARTY-DOUBLE, C. 5254*
LEONARD, A. 4933*	LUBIN, F. 5367	MARTY, M. 5056*
LEONARD, C.M. 5171*	LUKES, R.J. 5205	MASHBURN, L.T. 5383*
LERDY, J.-P. 5219*	LUNSCKEN, C. 5274*	MASON, D.Y. 5158*
LESLIE, G.A. 5093	LYLES, J. 5043	MASTRANGELC, M.J. 5100
LETNANSKY, K. 5325	LYSGAARD-HANSEN, B. 5293*	MASUDA, H. 4924*
LEUTHOLD, E. 5230*	MABUCHI, M. 4924*	MATARESE, G.P. 5062*
LEVDIK, T.I. 4996*	MACARIO, A. 5166*	MATHE, G. 4841*
LEVENTHAL, B.G. 4840*	MACDONALD, P.C. 5268*	MATSUGUCHI, T. 4966*
LEVINE, A.S. 5034	MACKAY, I.R. 5104	MATSUI, N. 4924*
LEVINE, G.D. 5202	MACKAY, L. 5092	MATSUMURA, K. 4927*
LEWIS, A.M., JR. 5034	MACLEOD, M.C. 5329, 5331	MATSUO, T. 5214
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LI, F.P. 5292*	MAINS, R.E. 5366	MATTHEIEM, W.H. 5365
LIANG, W. 5095	MALAISE, E.P. 5018	MATTHEWS, M.B. 5001
LIDIN, B. 5083	MALAVEILLE, C. 4953*	MATTISON, R.A. 5162*

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MAYOR, H.D. 4999	MILLER, E.C. 4859	MONTESANO, R. 4953*
MAYYASI, S.A. 5043	MILLER, G. 5230*	MOORE, G.E. 5306
MCALLISTER, R.M. 5007, 5009	MILLER, J.A. 4859	MOORE, M. 5084
MCBRIDE, C. 5328	MILLER, J.J. 5121	MORALES, A. 5259*
MCCALLA, D.R. 4867	MILLER, T.E. 5168*	MORI, H. 4925*
MCCLUNG, J.E. 5012	MINTZ, B. 5210	MORI, S. 4918*
MCCOY, J.L. 5171*	MIRAND, E.A. 5063*	MORIOKA, A. 5139*
MCCOY, M.G. 5014	MITAUYAMA, M. 4956*	MOROOKA, H. 5186
MCCULLOCH, E.A. 4908	MITTWOCH, U. 5200	MORPURGO, G. 4954*
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MCKHANN, C.F. 5079	MIYAKAWA, M. 4971*	MORRISON, D.M. 4938*
MCMAMARA, D.J. 5362	MIYASAKA, K. 4960*, 4961*	MORRISON, J.C. 4938*
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MEIERHENRY, E.F. 5260*	MIYATA, Y. 4922*, 4927*	MOSSELMANS, R. 5303
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MENAUULT, M. 5234*	MODAK, M.J. 5051*	MUIR, C.S. 5299*
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METZGER, H. 4947*	MOHR, U. 5218	MUNZAROVA, M. 5069
MEUWISSEN, J. 4851*, 4910*	MOHRI, N. 5206	MURAKAMI, T. 4955*, 4957*
MEYER, G. 5144*, 5173*	MOLIN, L. 5275*	MURASKO, D.M. 5010
MEYER, J.S. 5375*	MOLL, T. 5093	MURGITA, R.A. 5113
MIAN, N. 5359	MOLLA, M.A.R. 4993*	MURPHY, G.P. 5109
MICHAEL, R.O. 4905*	MOLLER, G. 5333	MURPHY, M.L. 5207
MICHALOPOULOS, G. 5344	MOLLET, P. 4945*	MUSHINSKI, J.F. 5395*
MICHAUD, J.L. 5258*	MONAHAN, T.M. 5119	MUSSINI-MONTEPELLIER, J. 5258*

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NAGAI, T. 5133*, 5135*	NILES, R.M. 5310	OMORI, Y. 4915*
NAGAMACHI, Y. 4963*	NIND, A.P.P. 5190	ONGE, T. 4917*
NAGAO, M. 4912*	NISHI, Y. 4914*	OPPENHEIMER, S.B. 5122
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NAKADATE, M. 4897	NOBLE, R.L. 4874	OSBORN, M. 5035
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NAKAKUKI, K. 5124*	NOMURA, S. 5021	OSIPOVA, E.N. 5390*
NAKAMURA, T. 4956*, 4963*	NORPOTH, K. 4888	OSTROWSKI, W. 5109
NAKANISHI, K. 4970*	NORWOOD, T.H. 5336	OVE, P. 5343
NAKANO, G. 4963*	NOWINSKI, R.C. 5118	OWENS, E.J. 4823*
NAKATSUGAWA, K. 5347	NUGMANOV, S.N. 5279	PAGES, A. 5254*
NAKAYAMA, I. 5214	NUSSE, R. 5175*, 5176*	PAL, B.K. 5037
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NAOE, S. 4924*	OBERLING, F. 5246*	PARK, W.D. 5386*
NEAVES, W.B. 5308	O'BRIEN, T.G. 4869	PARKER, C.W. 5073
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NELSON, D.S. 5148*	O'CONNOR, P.J. 4893	PASCU, L. 4903
NEMOTO, T. 5160*	O'CONNOR, T.E. 5055*	PASQUALI, F. 5089
NESPOLI, L. 5089	OESCH, F. 4937*	PASTAN, I. 5068
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NEWSOME, H. 5288	OKADA, M. 4892	PAUL, W.E. 5075
NEWTON, M. 4873	OKAMOTO, T. 4918*	PAVIE-FISCHER, J. 5085
N'GUYEN TRUNG LUONG 5300*	OKANO, P. 5055*	PAYMASTER, J.C. 5282
NIAUSSAT, P.M. 5300*	OKITA, K. 5138*	PECEVSKI, J. 4981*
NICOLINI, C. 4813	OKUDA, K. 5192	PECKA, Z. 5288
NICOLL, J.W. 4860	OLD, L.J. 5245*	PEDERSEN, N.B. 5232*
NICOLSON, G.L. 5320	OLESEK, D. 5152*	PELFRENE, A. 5220*

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PENDERGRASS, W.R. 5336	PREUD'HOMME, J.L. 5241*	RICH, R.R. 5114
PERIES, J. 5052*, 5056*, 5099	PREUSSMANN, R. 4983*	RICHMOND, C.R. 4830*
PERK, K. 5025	PRICHARD, J. 5082	RIEGER, C.H.L. 5102
PERRY, A. 5050*	PRIMUS, F.J. 5103	RINDE, E. 4911*
PERSSON, K. 5318	PRIS, J. 5236*	RINDICH, A.V. 5393*
PERSSON, U. 5333	PRODAN, L. 4903	RITCHIE, J.W.K. 5278
PETER, H.H. 5085	PRODI, G. 5166*	ROA, R.C. 5024
PETER, S. 4932*	PROPST, A. 5269*	ROBERSON, M. 5122
PETERSON, A.R. 4939*	PROTA, G. 4857	ROBERTS, J.P. 5201
PEZOLD, B. 4972*	PUVION, E. 5321	ROBINS, R.A. 5145*
PHILLIPS, E.R. 5165*	QUADRIFOGLIO, F. 4857	ROBINSON, C.R., JR. 5050*
PIECZYNSKI, W. 4906*	QUINTANA, M. 5254*	ROCHICCIOLI, P. 5253*
PIENKOWSKA, K. 5316	RAJALAKSHMI, S. 4905*	ROCHMAN, H. 5102
PIEROTTI, M.A. 5026	RAJEWSKY, M.F. 4899	ROGERS, A.E. 5149*
PIERRE, R.V. 5208	RALL, D.P. 4852	ROHRBORN, G. 4822*, 4948*, 4974*
PIHL, E. 5190	RALPH, P. 5082	ROMUALDEZ, A.G., JR. 5094
PISLARU, V. 4903	RANADIVE, K.J. 5364	RORSMAN, H. 5318
PITOT, H.C. 5344	RAO, D.N. 5282	ROSAI, J. 5202
POCHIN, E.E. 5290*	RAO, R.S. 5081	ROSE, D.P. 4875
PODLIASHCHUK, E.L. 4987	RATZAN, R.J. 5382*	ROSENBERG, N. 5017
PODOLSKY, D.K. 5355	RAY, M. 5209	ROSENBERG, R.N. 5357
POGOSIAN, A.S. 5390*	REDDY, C.R.R.M. 5182	ROSENGREN, A.M. 5318
POIRIER, R. 5296*	REES, D.A. 5265*	ROSENGREN, E. 5318
POLIKARPOVA, S.N. 5327	REES, J.A. 5121	ROSENKRANZ, H.S. 4868
POLLIACK, A. 5202	REFETOFF, S. 5102	ROSSI, G.B. 5062*
POREBA, R. 5276*	REGEZI, J.A. 5250*	ROTH, J.A. 5111, 5252*
PCRTEOUS, D.D. 5172*	REGNIER, C. 5236*	ROUBIN, R. 5085
POTTEP, M. 5075	REICH, E. 5032	ROWLANDS, D.T., JR. 5147*
POVEY, S. 4896	REISFELD, R.A. 5177*	RUBENSTONE, A.I. 5204
PRABHAKAR, B.R. 5295*	REITZ, M.S., JR. 5006	RUGGIERI, S. 5396*
PRABHAKAR, H. 5295*	REIZENSTEIN, P. 5238*	RUMEAU, J.-L. 5236*
PRASAD, K.N. 5350	REZNIK, G. 5218	RUSSELL, E.R. 5025
PREHN, L. 5310	REZNIK-SCHULLER, H. 5218	RUSTIA, M. 4973*

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RUZICKA, P. 4932*, 4976*	SCHAEFER, H.E. 4839	SEKIGUCHI, S. 5139*
RYD, W. 4871	SCHAEFER, O. 5297*	SEKIZUKA, H. 4955*, 4957*
SAAL, F. 5052*	SCHAUBHUT, C.W., JR. 5260*	SELL, S. 5315
SABHARWAL, B.D. 5295*	SCHECHTER, I. 5397	SEMAN, G. 4810
SACCHI, N. 4982*	SCHEIDTMANN, K.-H. 5002	SENGUPTA, S.R. 5185
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SACHS, V. 5368	SCHER, C.D. 5017	SEYFER, A.E. 5201
SAEGER, W. 5272*	SCHIRRMACHER, V. 5155*	SHABAD, L.M. 4827*
SAITO, M. 5146*	SCHLOM, J. 5065*	SHACKS, S.J. 5070
SAITO, T. 4966*, 4968*	SCHLUTER, D.N. 5374*	SHAH, P.N. 5322
SAKAKIBARA, K. 5123*	SCHMID, M. 5194	SHANMUGARATNAM, K. 5013
SAKASHITA, T. 5186	SCHMID, W. 4984*	SHAPIRO, N.I. 5040
SAKURAI, T. 5137*	SCHMIDT, N.J. 5098	SHAPOSHNIKOV, I.A.D. 5398*
SALOMON, C. 5058*	SCHMOYER, M.E. 5314	SHAPOT, V.S. 5388*
SAMBROOK, J. 5000	SCHNEIDER, F. 5360	SHARKEY, R.M. 5133
SANDBORN, E.B. 5273*	SCHNEIDER, P. 5212	SHARP, P.A. 5000
SANDBRINK, H. 5369*	SCHOCHETMAN, G. 5065*	SHEARER, G.M. 5067
SANDERS, B.G. 5163*	SCHOEN, L.H. 4838*	SHEARER, W.T. 5073
SANDRITTER, W. 5338	SCHOR, N.A. 5379*	SHEI, M. 5247*
SANO, M. 5186	SCHOUR, L. 5181	SHENK, T.E. 5038, 5042
SANO, T. 4958*	SCHULTZ, R.M. 5131	SHERTON, C.C. 5019
SANTOS, G.W. 5110	SCHUSTER, S.M. 5348	SHETH, A.R. 5364
SANYAL, B. 5298*	SCHWANITZ, G. 4951*	SHETH, N.A. 5364
SARAVIS, C.A. 5149*	SCHWARTZ, A.G. 4877	SHIBASAKI, K. 5106
SARMA, D.S.R. 4905*	SCHWARTZ, J. 5153*	SHIBATA, K. 4923*
SASAJIMA, K. 4958*	SCHWARTZ, R.S. 5120	SHIBLEY, G.P. 5050*
SASAKI, O. 4966*	SCHWARTZ, S.O. 5204	SHIMIZU, T. 4962*
SASAKA, I. 4925*	SCHWARZENBERG, L. 4841*	SHIMOJO, H. 5053*
SATO, E. 5188	SCHWARZFISCHER, F. 5361	SHIMOSATO, Y. 4958*
SATO, K. 4915*, 4962*	SEGA, E. 5180*	SHIRAI, T. 4922*, 4970*
SATO, M. 5188	SEHON, A.H. 5086	SHIRAKABE, H. 4960*, 4961*
SATO, S. 5349	SEIDMAN, I. 4861	SHURGIN, A. 5174*
SAVATENKO, V.G. 5283	SEILER, J.P. 4943*	SIEGEL, C. 4870
SAVKOVIC, N. 4981*	SEINO, Y. 4912*	SIEGEL, S.E. 5034

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SILVA, J.S. 5171*	STEEL, C.M. 4896	SUNAKAWA, M. 4957*
SIMES, R.J. 5148*	STEEVES, R.A. 5360*	SURAIYA, J.N. 5364
SIMS, P. 4936*	STEGNER, I. 4975*	SUURKULA, M. 5090
SIMSIMAN, R.C. 4869	STEIN, G.S. 5039, 5386*	SUZUKI, E. 4892
SINGER, B. 4952*	STEIN, H. 5206	SUZUKI, H. 4923*
SIRAGANIAN, R. 4947*	STEIN, J.L. 5386*	SUZUKI, K. 4960*
SIRBASKU, D.A. 4934*	STEPHENS, H. 5273*	SWACK, N.S. 4998
SIZARET, P. 5154*	STEPHENSON, J.R. 5008, 5022	SWENBERG, J.A. 5047*
SKARBERG, K.O. 5238*	STEPHENSON, M.L. 5045*	SYMES, M.O. 5121
SKELLY, H. 5315	STERLING, T.D. 4805	SZEPSENWOL, J. 5273*
SKIPSKI, V.P. 4817	STEVENS, D.P. 5104	SZIRMAI, E. 5368
SKURZAK, H.M. 5383	STLINGRAEBER, P.H. 5222*	TABACHNIK, B.I. 5279
SLADE, M.S. 5079	STOCK, C.C. 4817	TAGUCHI, T. 4964*
SLEEPER, K.M. 4873	STOHR, M. 5369*	TAHARA, E. 4965*, 5187, 5233*
SMADJA-JOFFE, F. 5018	STOLL, C. 5246*	TAJIMA, K. 5186
SMITH, S. 5345	STOSIEK, M. 4979*	TAKAHARA, O. 5214
SOBAJIMA, Y. 5129*	STRAULI, P. 5274*	TAKAHASHI, A. 4915*, 4964*
SOBHY, C.M. 4938*	STRELKOVA, R.M. 5280	TAKAHASHI, M. 4959*, 4970*
SOBIS, H. 5211	STRICKHART, F.S. 4887	TAKAMI, M. 4964*
SODEMOTO, Y. 4915*	STRICKLAND, S. 5032	TAKANO, M. 4855
SCEJIMA, K. 4966*	STROBER, W. 5087	TAKAOKA, T. 5123*
SOGA, J. 5186	STUDER, H.J. 5199	TAKASO, K. 5188
SOHAL, J.E. 4839*	SUCIU, I. 4903	TAKEDA, T. 5188
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SORRENTINO, J.M. 4934*	SUGIHARA, K. 4955*, 4957*	TAMAKI, N. 5115
SOULE, E.H. 5213	SUGIHARA, S. 4922*	TAMBOURIN, P.E. 5018
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SPECK, W.T. 4868	SULLIVAN, A. 5064*	TANAKA, K.K. 5127*
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TANNENBAUM, M. 5252*	TRIPATHI, F.M. 5298*	VAN VENROOIJ, W.J. 5332
TANPHAICHITR, V.S. 5400*	TRIPPIER, M.F. 5216	VANDEPUTTE, M. 5211
TASHIRO, Y. 5115	TROLL, W. 4911*, 4977*	VANDREY, J.P. 5387*
TATEMATSU, M. 4922*, 4970*	TROWBRIDGE, I.S. 5105	VARGA, L. 5247*
TAVASSOLI, M. 5203	TSCHAHARGANE, C. 4854	VARKARAKIS, M.J. 5109
TAVITIAN, A. 5050*	TSCHUBEL, K. 5263*	VARNAVIDES, L.A. 5102
TAYLOR, D.M. 5346	TSOU, K.C. 5014	VAROTTO, M. 5167*
TAYLOR, H.W. 4895	TSUDA, H. 4959*	VARSHAVER, N.B. 5040
TAYLOR, M.J. 5049*	TSUDA, N. 5214	VASHSH, L. 5247*
TAZAWA, K. 5186	TSUJI, K. 5214	VASILE, C. 5180*
TAZIMA, S. 4962*	TSUKADA, H. 4921*	VELTRI, R.W. 5012
TENCHINI, M.L. 4982*	TU, Y. 4867	VICK, N.A. 5046*
TEPLITZ, R.L. 5163*	TUFFREY, M.A. 5071	VITETTA, E.S. 5112
TERAO, H. 5141*	TURIAF, J. 5234*	VIZA, D. 5066
TERAO, K. 4855, 4929*	TY, J. 4992*	VLADIMIRSKAYA, E.B. 5289
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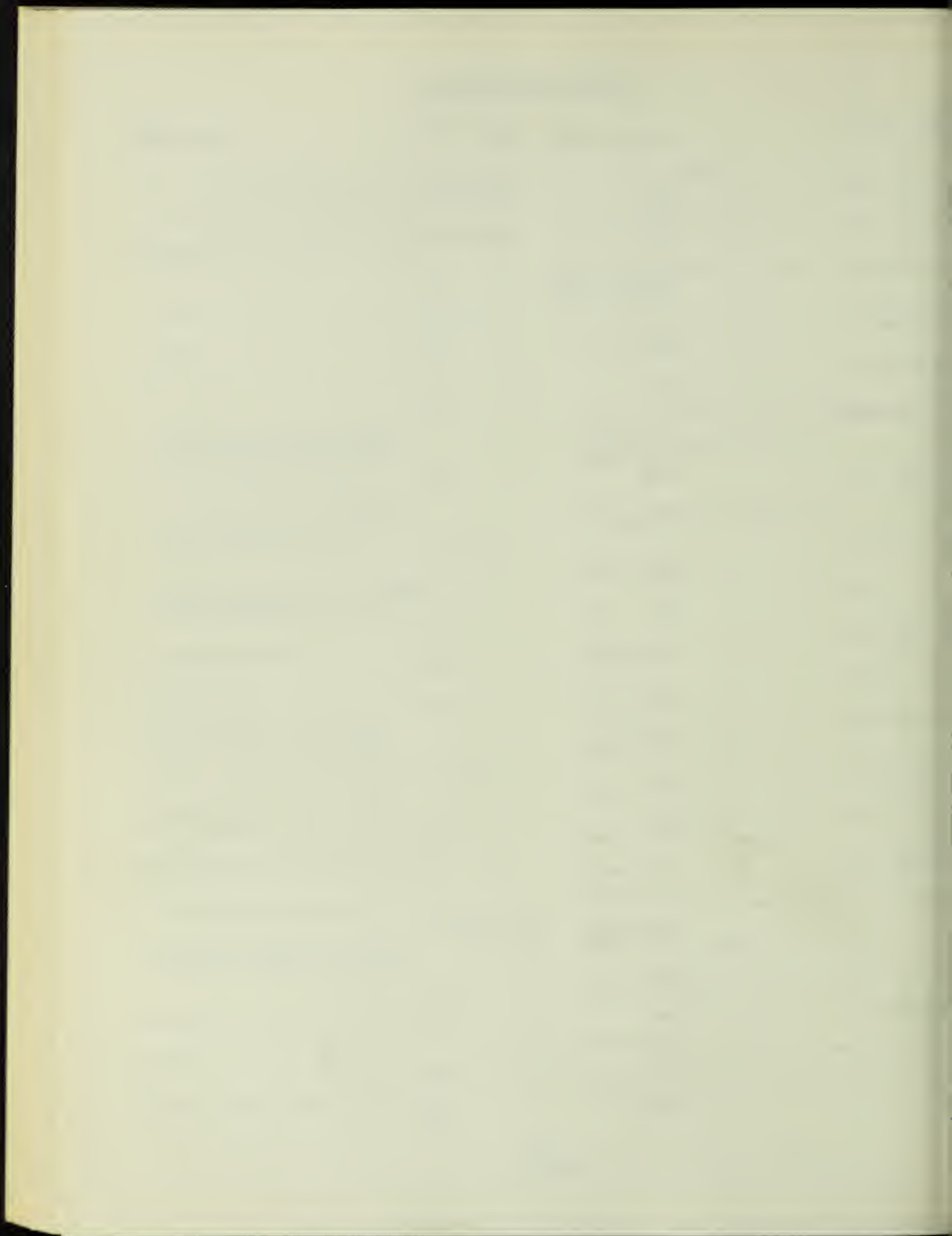
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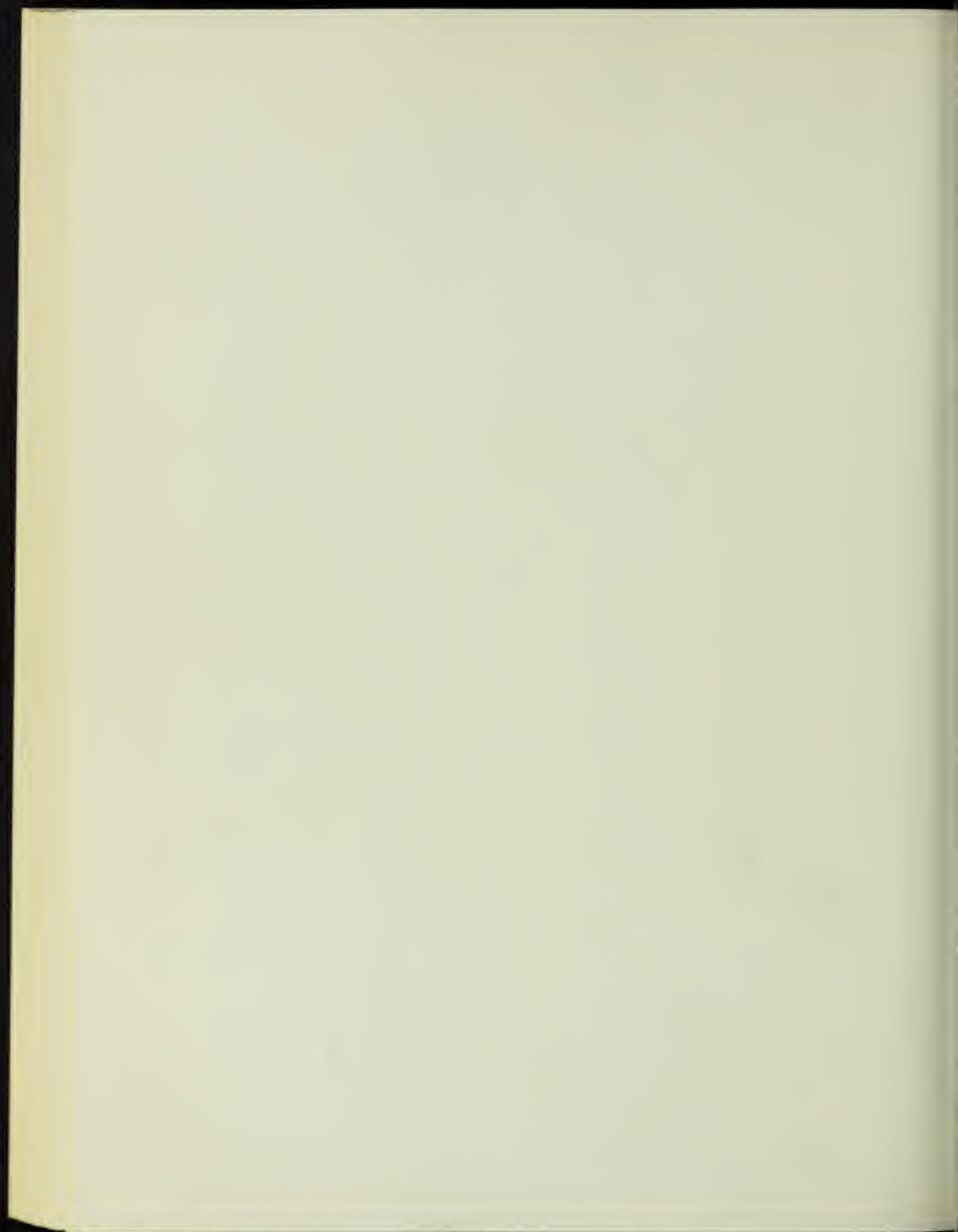
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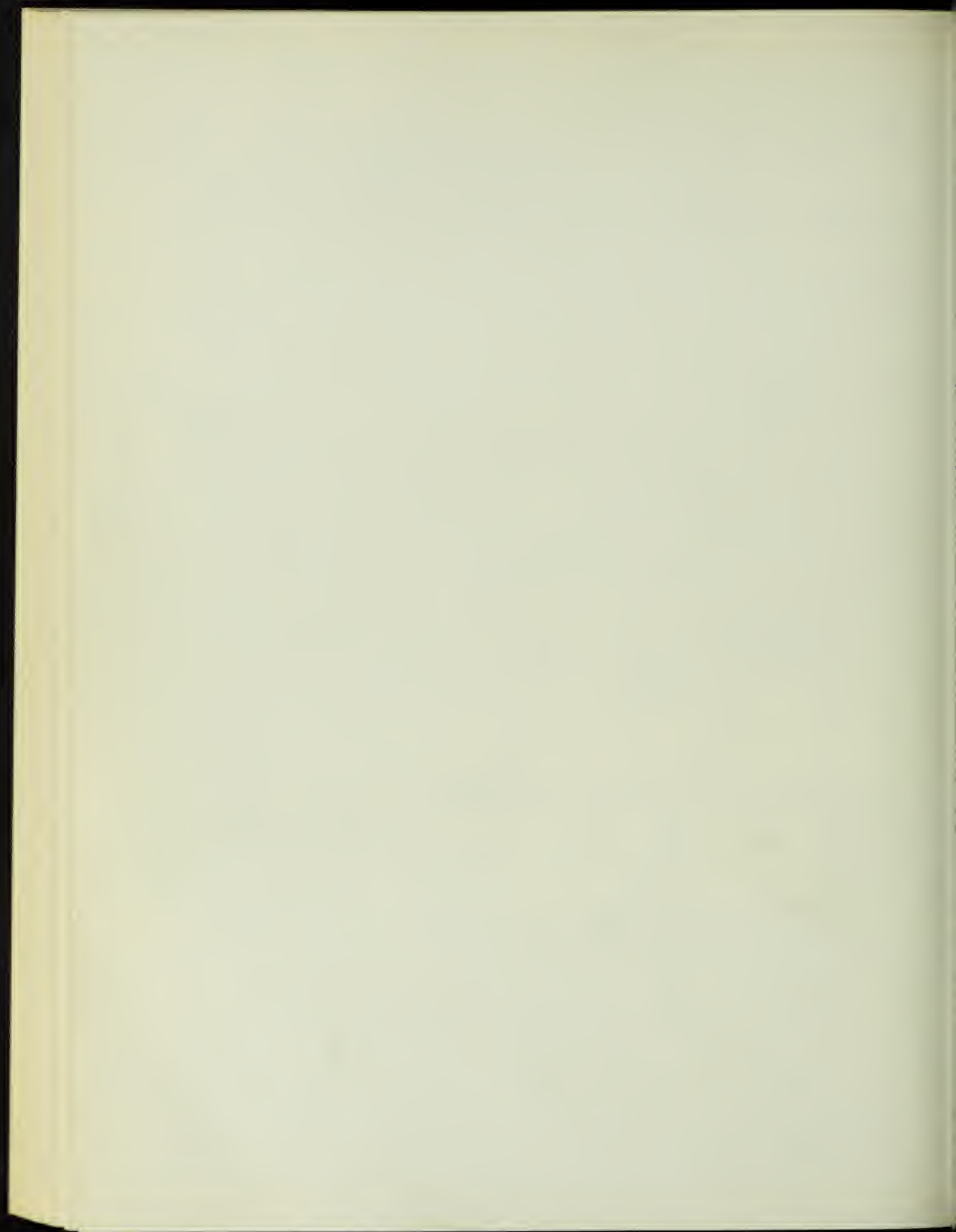
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**Vol. 13
No. 10**

CARCINOGENESIS ABSTRACTS

National Cancer Institute

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health



CARCINOGENESIS ABSTRACTS

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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

Carcinogenesis Abstracts is normally published monthly. Volume XIII covers the scientific literature published from Jan 1975 through Dec 1975. To increase the usefulness of *Carcinogenesis Abstracts*, Volume XIII, a Wiswesser Line Notation index and a Chemical Abstracts Service Registry Number index have been provided. These indexes reference compounds described in abstracted articles. A cumulative subject, author, CAS Registry Number, and Wiswesser Line Notation index for Volume XIII will be published shortly after the final regular issue.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations found in *Chemical Abstracts Service Source Index*, 1907-1974 Cumulative, are used. New journals are verified in *New Serial Titles* and abbreviated according to *International Standard ISO 833*. An asterisk indicates the author to address (other than the primary) in requesting reprints.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	Ind.	Indonesian
Ara.	Arabic	Ita.	Italian
Bul.	Bulgarian	Jpn.	Japanese
Chi.	Chinese	Kor.	Korean
Cro.	Croatian	Lav.	Latvian
Cze.	Czech	Lit.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
Eng.	English	Por.	Portuguese
Est.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fle.	Flemish	Ser.	Serbo-Croatian
Fre.	French	Slo.	Slovak
Geo.	Georgian	Spa.	Spanish
Ger.	German	Swe.	Swedish
Gre.	Greek	Tha.	Thai
Heb.	Hebrew	Tur.	Turkish
Hun.	Hungarian	Ukr.	Ukrainian
Ice.	Icelandic	Vie.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

A	angstrom(s)	M	molar
ACTH	adrenocorticotrophic hormone	mM	millimolar
ADP	adenosine diphosphate	μ M	micromolar
AMP	adenosine monophosphate	mOsm	milliosmolar
ATP	adenosine triphosphate	mEq	milliequivalents
BCG	Bacillus Calmette Guerin	min	minute(s)
bid	twice daily	mo	month(s)
C	degrees centigrade	MTD	maximum tolerated dose
cal	calorie(s)	N	normal concentration
kcal	kilocalorie(s)	NAD	nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADH	reduced nicotinamide adenine dinucleotide
Ci	curie(s)	NADP	nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NADPH	reduced nicotinamide adenine dinucleotide-phosphate
μ Ci	microcurie(s)		
cm	centimeter(s)	ng	nanogram(s) (10^{-9})
CNS	central nervous system	od	once daily
cpm	counts per minute	Pa	ambient pressure
dl	deciliter(s)	PAS	periodic acid-Schiff
ml	milliliter(s)	pg	picogram(s) (10^{-12})
μ l	microliter(s)	pgEq	picogram equivalent
DNA	deoxyribonucleic acid	po	orally
ED ₅₀	median effective dose	ppb	parts per billion
EDTA	ethylenediamine tetraacetic acid	ppm	parts per million
ESR	erythrocyte sedimentation rate	qid	four times daily
g	gram(s)	qod	every other day
kg	kilogram(s)	QO ₂	oxygen quotient
mg	milligram(s)	R	roentgen(s)
μ g	microgram(s)	RBC	red blood cells (erythrocytes)
Hb	hemoglobin	RNA	ribonucleic acid
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
ic	intracerebral	SGOT	serum glutamic-oxalacetic transaminase
icav	intracavitary	SGPT	serum glutamic-pyruvic transaminase
id	intra-dermal	SRBS	sheep red blood cells
ILS	increased life span	TCD	tissue culture dose
im	intramuscular	TCD ₅₀	median tissue culture dose
ip	intraperitoneal	tid	three times daily
ipl	intrapleural	U	unit(s)
it	intratumorous	mU	milliunit(s)
IU	International Unit	UV	ultraviolet
iv	intravenous	vol	volume
K _m	Michaelis constant	WBC	white blood cells (leukocytes)
LD	lethal dose	wk	week(s)
LD ₅₀	median lethal dose	wt	weight
m	meter(s)	x	times
mm	millimeter(s)	yr	year(s)

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REVIEW

- 5401 CONSIDERATIONS OF SOME CURRENT CONCEPTS IN CANCER RESEARCH. (Eng.) Moller, G. (Div. Immunobiology, Karolinska Institutet, Wallenberg-laboratory, Lilla Freskati, 104 05 Stockholm 50, Sweden); Moller, E. *J. Natl. Cancer Inst.* 55(4): 755-759; 1975.

Considerations of some concepts in cancer research are reviewed. These concepts are: 1) immune surveillance, and 2) that oncogenic viruses, chemical carcinogens, and physical agents can cause cancer by either directly transforming a large number of target cells or by suppressing the immune surveillance mechanism. Studies on clonality have revealed the monoclonal origin of tumors. Tumors are clonal for three possible reasons: 1) carcinogens only transform rare preexisting susceptible variants; 2) a large number of cells become transformed, but only one immunoselected variant becomes established; or 3) carcinogens accelerate the appearance of rare genetic changes leading to neoplasia. Some predictions are based on conventional immune surveillance as the following points show. Monoclonality of tumors is based on immune selection. Monoclonality of tumors does not occur in generally or locally suppressed individuals. Clonality should not occur in tumors induced *in vitro*. But *in vitro*-induced tumors should possess on the average stronger tumor-specific antigens. Immunodeficient individuals have an increased frequency of polyclonal tumors. Predictions not based on immune surveillance are two-fold: spontaneous tumors appear infrequently by genetic mechanisms analogous to somatic mutation and the first tumor cells to appear are not rejected by T cells which have other functions. The first tumor cells to appear are not recognized or rejected immunologically. Neoplasia is not particularly prevalent in patients with specific HL-A alleles. Hereditary neoplasms are polyclonal in patients with an intact immune system. (20 references)

- 5402 CARCINOGENS ARE MUTAGENS: A SIMPLE METHOD FOR DETECTION. (Eng.) Ames, B. N. (Biochemistry Dept., Univ. California, Berkeley, Calif.). *Proc. Int. Cancer Congr.* 11th. Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 54-57.

It is proposed that a sensitive and simple bacterial test for the detection of chemical mutagens in rat or human liver be extended to detect mutagenic metabolites in urine. The addition of commercial β -glucuronidase to petri dishes along with urine, liver homogenate, and bacteria (especially constructed mutants of *Salmonella typhimurium*) tester strains allows the detection of metabolites excreted as β -glucuronide conjugates. Mutagenic activity has been demonstrated in the urine of rats administered with a carcinogen, 2-acetylaminofluorene (200 μ g). The author suggests that this method be used for the screening of human urines to detect mutagenic metabolites of drugs and dietary compounds. It may also be useful for testing urinary metabolites of drugs and food additives in experimental animals.

In addition, the usefulness of the bacterial-mammalian microsomal assay for detecting carcinogenic activity of uncharacterized compounds in complex mixtures and the recent work involving the improvement of the sensitivity of the tester strains are discussed. The author suggests the replacement of one of the *S. typhimurium* strains, TA1536, with strain TA1000, which is more effective in detecting new type mutagenic activity. (13 references)

- 5403 RISKS AND BENEFITS OF ESTROGEN USE. (Eng.) Weiss, N. S. (Univ. Washington, SC-36, Seattle, Wash. 98195). *N. Engl. J. Med.* 293(23):1200-1202; 1975.

The average absolute risk of endometrial cancer in postmenopausal women is estimated to be 4-8-fold greater if the woman is receiving estrogen. However, estrogens do modify menopausal symptoms and apparently retard development of osteoporosis. One study indicates that the woman who is nonobese, parous, and nonhypertensive (thus at low risk) suffers the most increased risk from the use of estrogen. The only firm recommendation that can be given now is to closely monitor any woman with an intact uterus who is taking estrogens. (8 references)

- 5404 PLUTONIUM AND OTHER ACTINIDE ELEMENTS IN GONADAL TISSUE OF MAN AND ANIMALS. (Eng.) Richmond, C. R. (Los Alamos Sci. Lab., Univ. California, N.M.); Thomas, R. L. *Health Phys.* 29(2): 241-250; 1975.

Available information on the gonadal content of six mammalian species given various actinide elements by various routes of administration are summarized; emphasis is placed on plutonium. Although few data are available on biological changes resulting from plutonium deposition in gonadal tissue, experiments using rats and mice have demonstrated the response of the testes resulting in early lethality. Disruption of spermatogenesis and follicle damage has been reported for rabbits given 14-21 μ Ci/kg ^{239}Pu iv and ovarian damage has also been reported in mice. For single po doses of plutonium citrate or nitrate in one mouse and several pigs, the fraction of the administered burden in the gonads (FABG) has been reported on the order of 10^{-7} to 10^{-6} at relatively short times following acute exposure. The gonad content has been reported as a function of the form of plutonium sc implanted into large numbers of beagles; FABG values range from 1.5×10^{-4} for the nitrate form to 7.0×10^{-7} for the oxide form. Most available data come from experiments employing iv injections of plutonium. The average FABG value calculated from 15 iv injection experiments in five mammalian species is 3.0×10^{-4} , with only a factor of 10 between the highest and lowest values to account for differences between sexes or among species; the FABG value for human subjects is 2.2×10^{-4} . A comparison of FABG values for female and male rabbits has shown that the testes contained seven times more plutonium than the ovaries following an iv injection of plutonium nitrate. Inhalation of ^{238}Pu by female

mice and male and female beagles has been shown to result in average smaller FABG values than those observed from iv injection; FABG values range from 7.0×10^{-6} to 6.0×10^{-5} . Rabbits given im plutonium nitrate again have shown smaller average FABG values for females. Human studies have revealed gonadal fallout plutonium concentration values (0.5 pCi/kg) that were very similar to kidney, bone, and liver; these were slightly higher than lung, and lower than the lymph nodes. Thus, human gonads show no preferential concentration as compared with other tissues. Additional information on the gonadal concentration of other actinide elements in rats, dogs, and baboons have suggested FABG values similar to those observed for plutonium. (52 references)

- 5405 CANCER RISK AND ESTROGEN USE IN THE MENOPAUSE. (Eng.) Ryan, K. J. (Boston Hosp. for Women, Boston, Mass. 02115). *N. Engl. J. Med.* 293(23):1199-1200; 1975.

Some estrogens are produced from body fat during the menopausal years; the amount produced is proportional to total body weight, paralleling the increased risk of endometrial cancer with obesity. Two studies indicate that the risk of endometrial cancer is increased 5-14-fold by administration of estrogen. The increase in risk caused by obesity is estimated to be 3-9-fold. A protective effect of estrogen against heart disease has been largely discredited. Prior thromboembolic events, migraine headaches, family history of cancer and/or excessive smoking should be weighed as contraindications to estrogen use. (10 references)

- 5406 SOME RELATIONS BETWEEN TERATOGENESIS AND MUTAGENESIS. (Eng.) Kalter, H. (Univ. Cincinnati Coll. Medicine, Cincinnati, Ohio 45229). *Mutat. Res.* 33(1):29-36; 1975.

Some relations between teratogenesis and mutagenesis are reviewed. In teratology, genetic change as the result of congenital abnormalities is stressed while mutation deals with genetic damage induced by environmental agents (abnormalities of gross chromosome structure). The two types of genetic damage should not be equated. Two interesting distinctions between genetic damage and malformations concern the relation between the time and place of their origin; whereas genetic changes are environmentally induced, malformations are commonly diverse in origin. The type of malformation seldom reveals into which of these categories it falls. The only known chemical agents which cause both germ-cell changes and malformations are alkylators. The mechanism of action of all chemical teratogenic agents is probably different from that of chemical mutagens. Mutation implies a multigenerational accumulation. In malformation, the only transmissible elements are the preexistent genes that may be involved in susceptibility to the embryological effects of environmental agents. Genetic damage as opposed to the toxicological phenomena are linearly related to dose, and the linearity can be extrapolated to zero dose. In conclusion, environmentally induced malformations and mutations cannot be equated with each other and

used as mutual indicators in monitoring potential harmful effects of the environment. (20 references)

- 5407 ON THE POSSIBLE MECHANISM OF CARCINOGENIC ACTION OF VINYL CHLORIDE. (Eng.) Van Duuren, B. L. (New York Univ. Med. Cent., N.Y.). *Ann. NY Acad. Sci.* 246:258-267; 1975.

Relevant information bearing on the possible mechanism of action of the carcinogen vinyl chloride is summarized. The relationship of indirect-acting alkylating carcinogens and their direct-acting counterparts is described. It is suggested that an α -chloro ether or related chloronium ion intermediate is involved as an activated carcinogenic intermediate *in vivo*. Based on earlier studies it is also suggested that noncovalent binding to serum albumin, microsomal membranes, or other target sites may precede activation to a carcinogenic intermediate. Serum albumin binding may be related to the site of origin of acroosteolysis, a disease associated with exposure to vinyl chloride. Trichloroethylene is a widely used industrial chemical. Based on its structural similarity to vinyl chloride and known information concerning its metabolism in animals and man, an α -chloro ether or -onium ion is suggested as an important intermediate in its metabolism. It is likely to be carcinogenic, particularly to the liver but this remains to be established. Other chemical agents (e.g., dimethylnitrosamine, 1,1-dimethylhydrazine, diethylnitrosamine) that have been shown to be carcinogenic to animals and man are briefly mentioned. (51 references)

- 5408 CONTRIBUTIONS OF VIROLOGY TO ONCOLOGY. (Eng.) Stoker, M. G. P. (Imperial Cancer Res. Fund Lab., Lincoln's Inn Field, London, England). *Neoplasma* 22(3):243-249; 1975.

Contributions of virology to oncology are reviewed. Tumor viruses are studied for two main reasons: as agents of natural cancer, and as tools in general oncology. Viruses have proved to be invaluable for investigating the physiological changes in cancer cells. The study of virus transformed cells and untransformed controls is readily accomplished and the process can be studied by the use of revertants. Tumor viruses contain one or more "transformation genes" which are probably analogous to cancer genes. Correlations have been established between viruses and naturally occurring cancers as opposed to those experimentally induced. Among these "cancer-inducing" viruses, polyoma virus, simian virus 40 and herpes virus are well known. Marek's disease (herpes) induces lymphoma in chickens. Feline leucosis syndrome is also a viral cancer. Except in the case of benign papillomas, there is no clear proof of a viral cause of any human cancer. Burkitt's lymphoma, nasopharyngeal cancer and infectious mononucleosis all have the same virus present. Carcinoma of the cervix is paralleled with a positive herpes simplex type 2 test. There is no conclusive epidemiological or genetic evidence of viral transmission of leukemia and mammary cancer

in man, though B and C type particles are found in human milk and have been reported in leukemic tissue. It appears that oncogenes and/or virogenes are present in all cells and their activation by carcinogens is the general cause of cancer. (No references)

- 5409 ELEMENTARY ASPECTS OF RNA TUMOR VIRUS GENETICS. (Eng.) Vogt, P. K. (Sch. Medicine, Univ. Southern California, Los Angeles, Calif.); Duesberg, P. H. *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 220-225.

A survey of viral genome functions is presented, and the structure and organization of the genome are reviewed. The genome of RNA tumor viruses is divided into three functionally different regions which (1) direct virus replication, (2) direct cellular transformation, and (3) are required for both replication and transformation. Nothing is known about viral genes which direct and control the synthesis of progeny RNA. The best studied replicative functions of RNA tumor viruses are represented by the seven structural proteins of the virion; these include two glycoproteins occurring at the virion surface and five nonglycosylated proteins. The messenger RNA coding for structural proteins appears to be polycistronic, while a separate and independent messenger RNA is suggested for the glycoproteins. Four theses are advanced for the transforming functions of the RNA virus genome. Although evidence for the existence of a transforming viral protein is indirect, the location of transforming genes in about 12% of the viral genome is demonstrated by transformation-defective deletion mutants of sarcoma viruses. That neoplastic transformation by RNA tumor viruses is a consequence of virus genetic activity is indicated by the properties of temperature sensitive viral mutants; temperature sensitive avian sarcoma virus mutants also suggest transformation *via* only one viral gene. Besides replication and transformation functions, the viral genome also contains information needed for the synthesis of progeny virus and the neoplastic transformation of the cell; the viral RNA-dependent DNA polymerase is cited as the best example of such a coordinate gene function. Evidence derived from six lines of investigations favors a polyploid structure of the RNA viral genome. Measurements indicate a biochemical complexity of the RNA tumor virus genome corresponding to 3.5×10^6 daltons in RNA, but the radiation target size is much smaller than expected from viruses of the same RNA content. The minimal size of infectious double-stranded DNA in transfection experiments is estimated as 6×10^6 daltons for Rous sarcoma virus and single hit kinetics of infection are suggested. Noninfective sarcoma viruses segregate transformation defective and replication defective deletion mutants; a high frequency recombination *via* reassortment of genome segments or by crossing over is also found. Experimental results rejecting such a (polyploid) genome

model are also discussed. It is concluded that the majority of available data supports the idea of a polyploid genome of low complexity for RNA tumor viruses. (80 references)

- 5410 CELLULAR REGULATION OF HUMORAL IMMUNITY. (Eng.) Solomon, A. (Univ. Tennessee Memorial Res. Center, Knoxville, Tenn. 37920). *N. Engl. J. Med.* 293(18):928-929; 1975.

Multiple myeloma is distinguished by two types of B-cell abnormalities; uncontrolled proliferation of plasma cells, and reduction of the total capacity of immunoglobulin (Ig)-synthesizing B lymphocytes. Suppression of Ig synthesis by normal B cells resulted from co-culture of these cells with lymphocytes from 3 of 8 patients with immunodeficiency syndromes. Both T cells and monocytes or macrophages have been implicated in this suppression. The design of therapy for the impaired differentiation of B lymphocytes would provide another method of management for multiple myeloma. (10 references)

- 5411 THE IMMUNOLOGY, BIOCHEMISTRY AND BIOLOGICAL SIGNIFICANCE OF ONCORNAVIRUS INDUCED TUMOR CELL SURFACE ANTIGENS. (Eng.) Bauer, H. (Institut für Virologie, Fachbereich Humanmedizin, 6300 Giessen, West Germany); Rohrschneider, L.; Kurth, R.; Pauli, G.; Friis, R. R. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 211-217.

The immunological properties, expression, and biochemical characterization of tumor-specific non-virion cell-surface antigen (TSSA) are reviewed. Whereas its subgroup specificity is defined by the viral envelope antigen and cross neutralization between viruses of different subgroups does not generally occur, the avian leucosis and sarcoma virus complex is considered the most advantageous system for the study of TSSA. By using the immunological techniques of immuno-electron microscopy, immunofluorescence, and lymphocyte and humoral antibody cytotoxicity tests, normal chick embryo cells (CEC), avian leucosis virus (ALV)-infected CEC, and avian sarcoma virus (ASV)-infected and transformed CEC were compared. The various techniques indicated that TSSA were detectable in all ASV tumors or ASV-transformed cell cultures, were absent from normal CEC or ALV-infected, untransformed CEC, and were group specific for all ASV strains tested. TSSA cross reacts between ASV tumors produced after infection of different species; a group specificity of TSSA is also suggested by various *in vivo* experiments. All experiments have indicated that TSSA expression is under the genetic control of the virus. The investigation of TSSA expression in CEC infected by temperature sensitive mutants defective for transformation at the nonpermissive temperature is described. The results of focus formation, colony formation in soft agar, 2-deoxyglucose uptake, saturation den-

sity, and TSSA expression are tabulated and explained by assuming that TSSA is a necessary but insufficient prerequisite for cell transformation. No strict correlation exists between expression of TSSA and the various parameters used to describe the transformed state of the cell. A biochemical and biophysical characterization of TSSA identifies two distinct fucose-containing components (gp 85 and gp 37) identical with the viral envelope glycoproteins, and a third large component (molecular wt 100,000) believed to represent TSSA. The results indicate progress in the isolation and characterization of the first TSSA component to be recognized in a tumor virus system. (23 references)

- 5412 CELLULAR APPROACH TO TUMOR SPECIFIC ANTIGENS. (Eng.) Bubeník, J. (Inst. Experimental Biology and Genetics, Czechoslovak Acad. Sciences, Prague 6, Czechoslovakia). *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 232-237.

In vitro studies of tumor-associated transplantation antigens (TATA), tumor-associated membrane antigens (TAMA), and tissue type specific antigens (TTSA) are reviewed. Cellular immune response to the TATA is similar to the reaction against transplantation alloantigens; the lymphocyte response to mouse H-2 alloantigens is described. A series of secretory synthetic and metabolic processes triggered off in the effector cells lead to increased permeability of the target cell membrane, arrested intracellular and membrane transport, and target cell lysis. It is suggested that the lymphocyte sensitized against TATA or TAMA probably exerts its "cytotoxic" function in a similar manner, and that the role of macrophages in the cytotoxic reaction against TATA is analogous to that in its reaction against transplantation alloantigens. TTSA have been detected in experimental and human tumors, as exemplified by a transitional cell carcinoma of the urinary bladder. Urinary bladder carcinomas contain TTSA which stimulate the cellular and humoral component of the immune response; specific cytotoxicity of lymphocytes obtained from the blood of patients with bladder carcinoma has been independently confirmed. Data on the cytotoxicity and the specificity of the cytotoxic effect of lymphocytes from patients with urinary bladder carcinomas have been tabulated. A more detailed characterization of the lymphoid effector cell subpopulations has revealed the involvement of non-T cells carrying immunoglobulin (Ig) receptors and receptors for the Fc portion of Ig. A positive correlation between the tumor burden and the leucocytotoxicity of the patient has been indicated; therapy of bladder tumors appears to influence the lymphocytotoxic reaction by causing alteration in the amount of tumor material in the body. However, the importance of the cellular immune response against TTSA to the body's defense against tumor cell invasion has not yet been elucidated. (52 references)

- 5413 ANTIGENIC DETERMINANTS ON CARCINOEMBRYONIC ANTIGEN: CHEMICAL AND IMMUNOLOGICAL STUDIES. (Eng.) Egan, M. L. (City Hope Natl. Medical Center, Duarte, Calif. 91010); Coligan, J. E.; Morris, J. E.; Schnute, W. C., Jr.; Todd, C. W. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 244-248.

Chemical and immunological studies on the structure of carcinoembryonic antigen (CEA) are reviewed. CEA is a glycoprotein composed of 35-46% protein and 45-57% carbohydrate, with a molecular wt of 175,000. Determination of amino acid composition via p-toluene-sulfonic acid hydrolysis gave up to 30% higher yields than the HCl method for several of the amino acids present in CEA, and indicated the presence of 0.2-1 M of tryptophan/100 residues. A direct correlation has been found between the amount of mannose and protein content in various samples of CEA; galactose is the predominant neutral sugar, N-acetylglucosamine is the most concentrated of all sugars present, and sialic acid content is the most variable. The amino acid and carbohydrate compositions of various CEA preparations are tabulated. Studies on the immunological activity of CEA after sequential destruction of the carbohydrate residues by Smith degradation have suggested that essentially all the sialic acid is attached to the three position of galactose. Destruction of 100% of the fucose and sialic acid, 75% of the galactose, 50% of the mannose, and 50% of the N-acetylglucosamine did not significantly effect inhibitory activity in the radioimmune assay; however, 70% of the antigenic activity was lost after the acid hydrolysis step in the Smith degradation. The equality of the functional and intrinsic affinities found excludes bivalent binding as a factor in the CEA assay. Trypsin digestion of the CEA protein chain has indicated that the molecule does not contain more than one polypeptide chain. Separation of modified cysteine-cleaved polypeptides on Sephadex G200 illustrates that the carbohydrate is distributed throughout the fractions, but the antigenic activity is associated only with the smaller fragments. Further results indicate the presence of more than one antigenic determinant on the CEA molecule and suggest an important role for the protein portion. (16 references)

- 5414 EFFECTOR MECHANISMS IN TUMOR IMMUNITY: *IN VITRO* AND *IN VIVO* STUDIES. (Eng.) Cerottini, J. C. (Swiss Inst. Experimental Cancer Res., Lausanne, Switzerland); Plata, F.; Brunner, K. T. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 254-257.

The complexity of the *in vitro* tumor immunity interactions is described, and the relevance of the *in vitro* reactions to *in vivo* protective immunity

is discussed. Four model systems are described and schematically represented; these are: complement-mediated lysis, antibody-dependent lysis, lysis by sensitized thymus dependent (T) cells, and cell-mediated lysis *via* activated macrophages. Several studies on the humoral and cell-mediated immune responses of mice inoculated with the Moloney sarcoma virus (MSV) are described. Studies of the cell-mediated response have shown significant cytotoxic activity in the spleens and lymph nodes shortly after virus injection, no demonstrable activity at the time of maximal tumor size, and a later reappearance of cytotoxic activity. Conflicting results were obtained when the same lymphoid cell population was tested for cell mediated cytotoxicity using two different assay systems; both T and non-T lymphoid cells, T cells alone, and non-T cells alone are implicated. A further complexity is suggested by recent studies on the *in vitro* generating of cytolytic T lymphocytes (CTL). These results suggest that the spleens of mice resistant to MSV challenge, although containing no detectable CTL, have an increased number of CTL precursor cells as compared to normal spleens. A qualitative difference in the responsiveness of normal and immune spleen cells in mixed leukocyte cultures has also been noted. Taken together, the *in vitro* studies of the humoral and cell-mediated responses in the MSV tumor system show the existence of at least four different possible reaction mechanisms, i.e. lysis by antibody and complement, by antibody and killer cells, by immune non-T lymphoid cells, and by restimulated memory T cells. In the MSV tumor system, both serum and lymphoid cells from immune mice confer protection *in vivo*. Although *in vitro* studies indicate that the effector cells belong to non-T lymphoid cells, transfer experiments suggest that only T cells from immune spleens are able to protect irradiated recipients. Similarly, immune spleen cells restimulated in mixed leukocyte-tumor cell culture are able to confer resistance to mice injected with leukemia cells. However, other possible mechanisms of exerting such a protective effect are also still considered. (26 references)

- 5415 ESCAPE FROM SURVEILLANCE. (Eng.) Stanley, N. F. (Dept. Microbiology, Univ. Western Australia, Perth, Western Australia, Australia). *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 270-274.

The concept of immune surveillance is described, possible mechanisms of escape from surveillance are postulated, and an analysis of three human cancers associated with herpes virus is presented. Animal and human observations used to support the concept of immune surveillance have cited the increased incidence of malignant disease in infancy and old age and the acquired and congenital immunodeficiency diseases. Studies on genetically predetermined defects indicate that genes may control the immune response against some antigens and suggest that malignancy arises when malignant cell clones

possess antigens with which the immunological apparatus is genetically not programmed to react effectively. In addition to genetically determined unresponsiveness, studies of host immune deficiencies have also cited the effects of experimental immune suppression by neonatal thymectomy, x-irradiation, and chemical immunosuppression. Other suggested possible mechanisms of escape from surveillance consider the malfunction of immune effector mechanisms, the "sneaking through" of tumor-associated antigens, refractoriness to immune effectors, and nonimmunological cell-membrane interactions. An analysis of Burkitt's lymphoma noted eight main pathological and epidemiological observations, indicated the multifactorial disease origin, and presented no hypothesis capable of explaining all the observations. Nasopharyngeal carcinoma patients display higher levels of antibody to Epstein Barr virus antigens than controls, suggesting a reflection of continuing Epstein Barr virus antigenic stimulation. Evidence that the suspected genetic predisposition to nasopharyngeal carcinoma involves genes within the major histocompatibility gene complex is also presented, and an escape mechanism involving serum blocking factors is suggested. While cervical carcinoma is found associated with herpes simplex virus type two and cytomegalovirus, the cancer rarity but virus ubiquity again precludes the postulation of any escape mechanism. (44 references)

- 5416 EMBRYONIC PROTEINS IN MALIGNANT NEOPLASMS. (Eng.) Klavins, J. V. (Queens Hosp. Center, Jamaica, N.Y.); Berkman, J. I.; Mesa-Tejada, R.; Weiss, M.; Krauss, E. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 200-207.

The significance of the expression of gene products in defining cancer specificity is discussed, and a tentative classification of pregerminal and germinal gene products is presented. The biochemical specificity of cancer is defined by: the presence of cancer specific gene products, the repression or deletion of gene products, the expression of pregerminal gene products and/or the expression of a specific set of gene products. In attempting to define cancer specificity by the expression of pregerminal or germinal gene products, two modalities of carcinogenesis are considered. The non-repression of embryonic protein synthesis is associated with some kind of block in normal differentiation, or with the derepression phenomena. A hypothetical relationship of gene products in differentiation and carcinogenesis is schematically illustrated and two variant forms of expression/derepression of gene products are suggested. While not a specific gene product in cancer, carcinoembryonic antigen has significant clinical application in monitoring patients with colon cancer during therapy. The microheterogeneity of α fetoprotein from cord blood has been demonstrated *via* DEAE cellulose column chromatography; two other proteins defined in human fetal serum, α 2H globulin and β S

glycoprotein, are also associated with malignant neoplasms. Other less investigated gene products of similar nature in man are also reported; on the basis of their presently known biological properties, these gene products are tentatively classified. Pregerminal gene products include: Regan isoenzyme, melanoma specific substances, glioblastoma specific substances, lung cancer substances, colon cancer substances inducing delayed hypersensitivity, and gastric cancer anemia-inducing substances. Germinal gene products are thought to include: carcinoembryonic antigen, α fetoprotein, fetal sulfoglycoprotein, fetal thymidine kinase, α 2H globulin, and β S glycoprotein. Numerous other undefined gene products are suggested, and the search for a single universal gene product in human malignant neoplasms is noted. (19 references)

- 5417 THE 12TH REPORT OF THE HUMAN RENAL TRANSPLANT REGISTRY. (Eng.) Barnes, B. A. (Organ Transplant Registry, 55 E. Erie St., Chicago, Ill. 60611); Bergan, J. J.; Braun, W. E.; Fraumeni, J. F., Jr.; Kountz, S. L.; Mickey, M. R.; Rubin, A. L.; Simmons, R. L.; Stevens, L. E.; Wilson, R. E. *J.A.M.A.* 233(7):787-796; 1975.

Current results of kidney transplantation in man are presented; results are summarized in five-year life-table analyses of recipient survival and graft function, while a summary of special studies is also provided. A total of 16,444 kidney transplants are registered and followup data is available for 14,479 patients; of those recipients, 46.8% are alive with a functioning graft, while an additional 20.6% survive without transplant function. There is an expected age distribution of recipients in the transplant population, but with a general bias toward males. The most frequent renal diseases leading to transplantation are glomerulonephritis, pyelonephritis, polycystic disease, and nephrosclerosis, while special reports on rare diseases causing the end-stage renal failure resulting in transplantation are also noted. The increasing use of cadaver organs in transplantation is noted, 70.4% of all grafts use cadaveric sources, while sibling donors continue to be as prevalent as parents. A longitudinal profile of gross results of first transplants reveals a decreasing mortality in primary transplantation; the sequence of grafting from a cadaver followed by grafting from a related donor has a better chance for long term success than the reverse situation, but sequential grafts from related donors have the best chance for success. Grafts from offspring showed superior functional success. In evaluating the transplantation procedures, both relative and cadaveric graft recipients having nephrectomy fare better than those retaining their own kidneys. Special problems of pediatric kidney recipients are also discussed: post-transplant complications note problems of fertility, higher death rates due to myocardial infarction and cerebrovascular accidents, and greater frequencies of reticulum cell sarcoma and other hemopoietic neoplasms than expected in the general population. More than 60% of the failed transplants are lost to rejection, while 40% of all deaths are due to sepsis. Analysis of 7,905 cases of

renal transplants and a correlation of survival with tissue matching notes a differential survival of 15-20% between transplants having none to four antigens in common. Patients with greater than 5% preformed antibodies have significantly fewer grafts functioning at seven days and subsequently. Previous trends are generally confirmed. Finally, a discussion of tissue typing is presented. (7 references)

- 5418 IMMUNOPATHOLOGY OF IMMUNOCYTOMAS. (Eng.) Drivsholm, A. (Bispebjerg Hosp., Copenhagen NV, Denmark). *Br. J. Haematol.* 31(Suppl.): 205-219; 1975.

The production of physiological and pathological immunoglobulins, pathogenesis, and clinical features of immunocytomas are reviewed. Immunocytomas are disorders in the B-lymphocyte series, characterized by production of an M-component. The production of M-components is discussed in relation to possible etiology and pathogenesis. The production of interferon and osteoclast activating factor is mentioned. Finally, the interrelationship of the immunocytomas is described on the basis of the hypothesis of Salmon & Seligman (1974), which relates the clinical syndromes to the pathway of B-cell differentiation. (86 references)

- 5419 THE NATURE OF THE IMMUNOLOGICAL INTERACTION BETWEEN THE HOST AND THE TUMOR. (Eng.) Alexander, P. (No affiliation). *Laryngoscope* 85(3): 487-490; 1975.

The complex host-tumor interaction at the immunological level, and various immune parameters of both the host and the tumor are discussed. The multifactorial process of "escape" involves some of the following factors: development of specific and permanent non-reactivity, generalized immune depression of the host, specific interference by humoral factors, and anatomical limitations. The main factors involved in interfering with the cytotoxic action are soluble tumor-specific transplantation type antigens (TSTA), which pre-empt the TSTA in the cell membrane and thus prevent interaction between target and aggressor cell. The importance of anatomical factors is illustrated through the localization of bacterial infections and the unequal expression of concomittant immunity. The role of immunity in metastatic spread is not considered to be the major factor in elimination of disseminated tumors. Evidence has been accumulating that immune parameters are also involved in determining the rate of spontaneous resistance in the non-immune suppressed host. A correlation has been observed for a series of animal tumors between the tendency to metastasize. Immunogenicity is defined as depending on two factors: the magnitude of the host response to the TSTA, and the effectiveness with which the inoculated living tumor cells manage to "escape". In a series of rat tumors, the efficient "escape" is the immune parameter which facilitates metastasis, and both metastasizing and nonmetastasizing tumors evoke host reactions of similar magnitude. It is speculated that microfoci "escape" and grow into me-

tastases when they are surrounded by an adequate screen of soluble TSTA molecules that intercept the immune effector processes. It is emphasized that factors determining metastasis are multiple, and escape from immune destruction is at most a contributory cause. (No references)

- 5420 KAPOSI'S SARCOMA: A BYPRODUCT OF TUMOUR REJECTION. (Eng.) Warner, T. F. C. S. (Mayo Clinic, Rochester, Minn. 55901); O'Loughlin, S. *Lancet* 2(7937):687-688; 1975.

Some literature pertinent to the origin of Kaposi's sarcoma is reviewed, and the following hypothesis presented. Kaposi's sarcoma may result from a chronic immunological reaction between antigenically altered lymphoid cells and normal lymphocytes. In the course of this local graft-versus-host (GVH) activity, an angiogenesis factor is liberated and intense proliferation of mesenchymal and endothelial cells ensues. During the GVH-like activity, an oncogenic virus is either transferred to or induced in the cells responsive to the angiogenesis factor. Thus, the stage is set for neoplastic transformation of these cells in an environment which is conducive to the growth of the virally transformed vasoformative mesenchyme. (43 references)

- 5421 KARYOLOGICAL INSTABILITY OF NEOPLASTIC SOMATIC CELLS. (Eng.) DiPaolo, J. A. (Natl. Cancer Inst., Bethesda, Md. 20014). *In Vitro* 11(2):89-96; 1975.

The role of chromosomal variability in neoplastic growth is evaluated. Noting the search for marker chromosomes and a characteristic chromosome constitution of the neoplastic cell, experiments citing the discovery of different chromosome complements of independent multiple tumors are acknowledged. Although a specific chromosome alteration is found in chronic granulocytic leukemia in man (the Philadelphia chromosome), the use of classical techniques shows that every cancer appears to be a specific dynamic entity characterized by cellular variability. Likewise, use of the standard Colcemid technique in analyzing chromosomes from chemically-induced tumors in Syrian hamsters reveals no detectable universal changes. Another study demonstrates that the chromosomal evolution depends upon the latency period of the individual tumors. Four categories of chromosome banding techniques are described, while current studies indicate that the interaction of dye with DNA, and the relationship between DNA and its associated nonhistone proteins, play important roles in banding formation. The newer techniques are applied to interspecific somatic cell hybrids, identify a translocation in chromosomes of cells of chronic granulocytic leukemia, and are used to examine numerical and structural deviations in the chromosomes of Syrian hamster cells. While the chromosomes of cultured normal Syrian hamster and human cells are noted to be stable, transformed cell lines and tumors display variable marker chromosomes. Different carcinogens produce transformations associated with

distinct but variable markers, indicating that structural changes at the chromosomal level are secondary and nonuniversal. Further analyses reveal randomly increased or decreased chromosome numbers, but similar constitutive heterochromatin in the normal and marker chromosomes. The findings are in contrast to the gene expression-suppression model of control of malignancy. Examination of nine variant BALB/3T3 cell lines fails to reveal specific chromosome distribution or recurring markers, while SA7 virus-transformed hamster cells also display no specific chromosomal alteration; it is again concluded that neither a common marker nor a specific numerical deviation characterizes such transformation. Likewise, *in vivo* or *in vitro* malignant transformation by dimethylbenzanthracene is not directly caused by gross abnormalities of the chromosomes. It is theorized that transformation and subsequent neoplasia are usually not associated with or due to an observable specific karyotypic abnormality, either in terms of a numerical imbalance or the formation of new marker chromosomes. (46 references)

- 5422 CHROMOSOMAL INSTABILITY AND MALIGNANCY. (Eng.) Schroeder, T. M. (Institut für Anthropologie und Humangenetik der Universität Heidelberg, Heidelberg, West Germany). *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 62-65.

The recognition and clarification of the connection between chromosome mutation in somatic cells and the predisposition to cancer is discussed. Cytogenetic findings such as marker chromosomes, the Philadelphia chromosome, and the loss of one No. 22 chromosome are indicative of a rearrangement of the genetic material at the onset of malignant growth, and of a clonal origin of neoplasms. Biochemical investigations in several types of cancer cells support the clonal development theory in many tumors: One of the two X-chromosomes in females becomes genetically inactive during embryogenesis. This relation between malignancy and chromosome instability is now being studied in four disease models: Fanconi's anemia, Bloom's syndrome, Ataxia teleangiectasia, and Xeroderma pigmentosum. These disorders share common symptoms such as chromosomal instability (spontaneously occurring in cell culture in the first three and induced by UV light in the latter); and high incidences of leukemia, cancer, carcinoma, and lymphoreticular neoplasia. Induced or spontaneously occurring chromosomal instability *in vitro* and *in vivo* leads to multiple mutations; these include point mutations as well as chromosomal mutations. Prospective changes in the blood cells (e.g., indicating the beginning of leukemia) are observable in the course of the disease. The consequences of these mutations could be an unbalanced karyotype, an altered cell that becomes the origin of a clonal cell population, and finally, the clonal cells might show up as tumor cells in a solid tumor or in leukemia cells.

Examples of clonal cells from different patients are presented. The development of such, or any other clone, into established tumor cells or leukemia cells has not yet been observed. However, observations made on disease with increased chromosomal instability may provide the key to the role of the chromosome mutation in carcinogenesis. (21 references)

- 5423 CYTOGENETIC FINDINGS IN LEUKEMIA. (Swe.) Mitelman, F. (Univ. Hosp., S-221 85, Lund, Sweden). *Läkartidningen* 72(37):3417-3421; 1975.

The pathogenic, clinical, therapeutic, and prognostic significance of chromosome studies in leukemias is reviewed. Philadelphia chromosome (Ph1) is present in about 90% of all patients with chronic myeloid leukemia, and even though it is detectable long before the first manifestation of hematological symptoms, it is not an inborn abnormality. There is substantial evidence indicating that Ph1 originates from a single transformed cell, i.e., that it represents a somatic mutation in a hematopoietic stem cell, and that chronic myeloid leukemia is of unicellular origin. The Ph1 is absent in other myeloproliferative syndromes. The chromosomal aberrations found in acute myeloid and lymphatic leukemia are also a result of an aberration, inherited in the bone marrow, in a stem cell common for granulocytes, erythrocytes, megakaryocytes, and monocytes. Chromosomal aberrations are present in about 50% of all pts. with acute myeloid or lymphatic leukemia. The chromosomal aberrations manifest themselves as an excess or loss of normally occurring chromosomes. While the chromosome number can vary from extreme hypodiploidy (below 46) to extreme hyperdiploidy (over 46) in acute myeloid leukemia, hypodiploidy is extremely rare in acute lymphatic leukemia, while chromosome counts over 60 are substantially more frequent in the latter than in acute myeloid leukemia. While Ph1 persists in chronic myeloid leukemia even during remission, abnormal cells are replaced by such normal karyotypes during remission from acute leukemias, and abnormal cells reappear during recurrence. Chronic lymphatic leukemia is believed to entail no chromosomal aberrations. (38 references)

- 5424 CUSHING'S DISEASE: A HYPOTHALAMIC FLUSH? (Eng.) Feldman, J. M. (Duke Univ. Medical Center, Durham, N. C. 27710). *N. Engl. J. Med.* 293(18):930-931; 1975.

Prior to 1952, 50% of patients with Cushing's syndrome died within five years of diagnosis. Advances in surgery and radiation therapy, and the availability of more effective antibiotics, have improved the prognosis in these patients. With the exception of those with adrenal carcinoma and the ectopic ACTH syndrome, most patients are helped by current therapy directed at the hyperfunctioning adrenal or pituitary gland. The procedures used include total adrenalectomy, conventional or proton beam radiation, and administration of the adrenocorticolytic drug 1,1-dichloro-2-(2-chlorophenyl)-2-

(*p*-chlorophenyl)ethane. To correct the basic defect in Cushing's syndrome will require a better understanding of the disturbance leading to overproduction of ACTH and also better methods to reduce a patient's cortisol secretion without leaving him totally dependent on corticosteroid replacement. Based on experimental evidence suggesting a CNS cause of Cushing's disease, Krieger *et al* treated their patients with the serotonin antagonist cyproheptadine. The patients had a prompt and sustained remission of their disease. The concept that cyproheptadine antagonizes hypothalamic serotonin in patients with Cushing's disease is strengthened by the ability of the drug to cause a 60% reduction in the exaggerated metyrapone response of patients with hyperserotoninemia from the carcinoid syndrome compared with a 32% reduction in the normal metyrapone response of healthy subjects. Cyproheptadine may be the primary therapy for patients with mild to moderate bilateral hyperplasia; may decrease the severity of hypercortisolism in patients with a primary tumor, and may ameliorate hypercortisolism in the 6-to 12-mo interval before radiation therapy exerts its beneficial results. (11 references)

- 5425 MALIGNANT OVARIAN CYSTOMAS: THEIR MANAGEMENT: A REVIEW AND AN ANALYSIS. (Eng.) Fichardt, T. (Dep. Radiother., H. F. Verwoerd Hosp., Pretoria, South Africa); Sandison, A. G. *S. Afr. Cancer Bull.* 19(1):32-60; 1975.

A review is given of the embryology, histogenesis, anatomy and physiology of the ovary and ovarian tumors. Their origin, possible etiology, pathology, spread, surgical staging, and histopathological grading are discussed. The revised classification of ovarian tumors proposed by a Committee of the World Health Organization (1973) was used. An analysis of 124 white patients with malignant ovarian cystomas, managed by means of six different treatment protocols of surgery, radiotherapy, and chemotherapy is included. The results do not suggest a 'best method' for future management. (33 references)

- 5426 CARCINOMA OF THE LIP. (Eng.) Wurman, L. H. (Ear, Nose, and Throat Associates, 614 First Street, Wausau, Wis. 55401); Adams, G. L.; Meyerhoff, W. L. *Am. J. Surg.* 130(4):470-474; 1975.

A review of 206 cases of lip cancer is presented, and particular attention is directed toward the problem of regional metastasis. A review of the literature is also presented. Of the 206 cases, only 8% did not use tobacco. Over 80% of the tumors occurred in persons with occupations that involved years of exposure to sunlight. Recurrences occurred in 19%, and 18% of these recurrences were multiple. A second primary lesion was noted in 19% of the 206 patients. Premalignant leukoplakia occurred in 7% of the cases. Lymph node metastases occurred in 5% of 129 lesions smaller than 2 cm, in over 50% of 21 lesions 2-4 cm, and in 73% of 11 lesions larger than 4 cm. Lymph node metastases developed in a total of 31 patients.

In six, regional metastases were present when they were first seen, and 25 metastases developed during the course of the disease. Of the 31 patients, 25 died of the tumor, two died of other diseases, and follow-up information was unavailable for two patients; the remaining two patients were alive and free of disease two years after radical neck dissection. The results suggest that the potential or actual presence of lymph node metastases may be of serious consequence, and that lip carcinoma may have a greater potential to metastasize than has been previously thought. (27 references)

5427 BIOCHEMICAL PROFILES OF HIGH RISK GROUPS.

(Eng.) Bulbrook, R. D. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, England). *Proc. Int. Cancer Congr. 11th.* Vol. 4 (*Cancer Campaigns, Detection, Rehabilitation, Clinical Classification*). Florence, Italy, October, 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 165-170.

The search for distinctive biochemical profiles in high cancer risk groups is reviewed with emphasis on hormone-related cancers. Of every 100 newly diagnosed cancers in women, nearly half arise in endocrine organs or in their target tissues (ovary, breast, uterus). In men, prostatic and testicular tumors account for some 14% of new tumors. Three traditional sources of information about potential risk factors are discussed: 1) studies with experimental animals, 2) classical epidemiology, and 3) biochemical investigations of patients with cancer. Results from many of the animal studies do not appear to be a reliable guide to the hormonal factors that may be of importance in the identification of women in high risk groups. Three main findings from epidemiological studies implicate estrogens in the etiology of breast cancer: 1) the increased risk associated with early menarche, and 2) with late menopause, and 3) a decreased risk associated with early oophorectomy for causes other than cancer. The classical risk factors identified by epidemiological surveys, however, do not appear to be useful enough for screening purposes. Two abnormalities have been noted in direct measurements of hormone status in patients with breast cancer: 1) increased thyroid stimulating hormone levels, and 2) subnormal excretion of androgen metabolites. A prospective study has been carried out in which urine specimens were collected from 5000 normal women and the amounts of androgen metabolites determined. It was found that the smaller the amounts of androgen metabolites excreted, the greater the subsequent risk of breast cancer. The high risk associated with a sub-normal excretion of androgens appears to be over-ridden by the "protective effects" of an early first child. Other studies have indicated that height and weight are important in a prospective study of breast cancer in post-menopausal women. Tryptophan metabolism has been found to be abnormal in patients with breast cancer. Epidemiological associations have been found between the incidence of breast, endometrial, and ovarian cancer suggesting that these

tumors may have some etiological features in common. It is concluded that the precise identification of women at high risk may require the simultaneous measurement of a number of factors and that a single all-embracing test may never be found. (30 references)

5428 EPIDEMIOLOGY OF NASOPHARYNGEAL CARCINOMA.

(Eng.) Ho, H. C. (Inst. Radiology, Hong Kong). *J. R. Coll. Surg. Edinb.* 20(4):223-235; 1975.

Findings related to the epidemiology of nasopharyngeal carcinoma were analyzed, and an etiological hypothesis compatible with the available data is postulated. This tumor has a high frequency in southern Chinese; the risk applies equally to first generation migrants to Southeast Asia, California, and Australia. However, recent reports suggest a decline in mortality from nasopharyngeal cancer in American-born Chinese. This trend, while not excluding a genetic determinant, points to the influence of environmental factors on the incidence of nasopharyngeal cancer. One factor in the genesis of the disease in the high-risk southern Chinese could be the ingestion of Cantonese salted fish, which contain appreciable amounts of dimethylnitrosamine. Two Caucasian patients treated for nasopharyngeal carcinoma at a Hong Kong hospital also had a history of consumption of salted fish. Genetic studies indicate that another etiological factor may be a second-locus histocompatibility antigen provisionally called Singapore-2. This new antigen appears closely linked to the hypothetical nasopharyngeal carcinoma susceptibility gene, and occurs more often in patients with nasopharyngeal cancer. A third factor may be infection by Epstein-Barr (EB) virus. Patients in Africa, Hong-Kong, Sweden, France, and the U.S. uniformly show a high EB virus-associated serological reactivity in relation to membrane, viral capsid, early, and soluble antigen systems. A high reactivity to the nuclear antigen is also found in Hong Kong Chinese patients. In Swedes and other population groups at low risk for nasopharyngeal cancer, the carcinogenic process may differ in all or some of the factors involved. The period of life when individuals are exposed to external factors that may play a role in the carcinogenesis also differs among low- and high-risk populations. It is unlikely that any one of the factors discussed can, alone, cause nasopharyngeal cancer; the etiology is probably multifactorial. (51 references)

5429 EPIDEMIOLOGICAL EVIDENCE CONCERNING THE TIME OF INITIATION OF CANCER IN CHILDREN.

(Eng.) Draper, G. J. (Dept. Social Medicine, Oxford Univ., Oxford, England). *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 150-155.

Evidence relating to the initiation of childhood cancer is reviewed and data from a study of such cancers in Britain is presented. In addition, the effects of suspected etiological factors were detected

ted and measured using a national registry of childhood tumors. The initiation of childhood cancer has been associated with obstetric radiography, evidenced by a marked dose-response relation. Viral infections, mainly influenza, during pregnancy have also been associated with childhood cancer. The poliomyelitis vaccination during pregnancy has been associated with subsequent tumors of neural origin in children. Other factors, such as congenital defects, particularly Down's syndrome, suggest a prenatal origin for childhood cancers, as does the small familial, possibly genetic, increase in risk. In families with one affected child, there is a slightly greater risk that the siblings will be affected by either the same disease or another tumor type. Thus, maternal infections seem to be related to the initiation of childhood cancer; however, it is not clear whether there is a direct association or whether it is due to the drugs used for treating the illness. Three epidemiological methods for classifying etiological factors in childhood were presented; retrospective case-control studies for low incidence diseases, prospective and quasi-prospective studies, and analysis of population incidence rates. Each method can be based on the use of a childhood tumor registry, except in the case of strong associations, i.e., diethylstilbestrol and vaginal cancer, but must cover a population of at least one million. (10 references)

- 5430 IMPORTANCE OF EPIDEMIOLOGICAL STUDIES RELATING TO HAZARDS OF FOOD AND ENVIRONMENT. (Eng.) Higgins, I. T. T. (Sch. Public Health, Univ. Michigan, Ann Arbor, Mich.) *Br. Med. Bull.* 31(3): 230-235; 1975.

Illustrative examples of the value of epidemiology are presented, and the use of epidemiological surveys in assessing various effects on the health of man is described. An initial discussion of the role of epidemiology in the evaluation of chemical hazards notes the emergence of etiological clues, the values of retrospective and prospective planned observations, and the suggestion of hypotheses and laboratory investigations. Epidemiological studies of illnesses associated with gross contamination, including outbreaks of infectious diseases and toxic poisoning, lead to the correlation of diseases with the causative agents alkylmercury, tri-*o*-cresyl phosphate, aniline dye, and vinyl chloride. Investigations of illness associated with occupational or accidental exposure to low concentrations of chemicals note the role of individual susceptibility and reveal the potential importance of cadmium exposure as a cause of cardiovascular disease. Further epidemiological studies indicate an inverse correlation between indices of water hardness and death rates from cardiovascular disease; such correlations are greatest for water calcium and carbonate, and apply to all the main subgroups of cardiovascular disease. Studies of environmental carcinogenesis elucidate the contribution of exposure to asbestos, nickel and chromate, aniline dyes, and ionizing radiation to subsequent development of lung cancer, respiratory cancer, bladder cancer, and lung cancer and leukemia,

resp. An epidemiological survey relating aflatoxin to liver cancer is discussed in detail, while the difficulties in assessing exposure and response are illustrated by studies of the incidence of cancer of the oesophagus and the hypothetical teratogenicity of blighted potatoes. However, environmental exposures and associations between cancer and congenital malformations are noted. The role and utilization of dose-response relations, and the need for monitoring and surveillance is discussed. Potential surveillance via cancer registries and record linkage is noted, and the need for combined laboratory measurements and total intake surveys is concluded. (24 references)

- 5431 OCCURRENCE OF NATURAL TOXINS IN FOOD. (Eng.) Crampton, R. F. (The British Industrial Biological Res. Assoc., Carshalton, Surrey, England); Charlesworth, F. A. *Br. Med. Bull.* 31(3): 209-213; 1975. (52 references).

The occurrence of natural carcinogens and toxic oxalates in food is briefly reviewed. While the carcinogens selenium, aflatoxins, and lower alkylnitrosamines have been identified in foods, a cause-and-effect relation has not yet been demonstrated. Aflatoxin intake of 8-300 ng/kg has been found to correspond to liver cancer incidences of 5-25/100,000 population/yr. However, the simultaneous occurrence of parasitic disease, malnutrition, and the consumption of crude alcoholic beverages and alkaloid-contaminated foods precludes a definite cause-and-effect relation of aflatoxin consumption and liver cancer. Two basic unresolved questions are that of a threshold dose and a latent period. Comparison of the effects of acute oxalate toxicity in domestic grazing animals, deliberate oxalate poisoning in experimental animals, and observations in man indicates that food oxalate does cause acute toxicity in man. Dietary oxalate is also associated with abdominal migraine in children. Thus, circumstantial evidence suggests that both oxalates and aflatoxins in food may contribute to chronic disease in man. (52 references).

- 5432 ANALYTICAL SURVEYS OF FOOD. (Eng.) Egan, H. (Lab. of the Government Chemist, London, England); Hubbard, A. W. *Br. Med. Bull.* 31(3):201-208; 1975. (49 references).

Following a brief history of food surveillance in the United Kingdom (UK), the strategy of food contamination surveys is discussed. These consist of studies of residues in the total diet, and selective studies on individual foodstuffs. The latter are made on the basis of the importance of the foods in the national diet, their liability to pesticide exposure, and known accumulative tendencies of the foods. Organochlorine pesticide studies have noted high dieldrin levels accumulating in the fat of insecticide-dipped sheep. Argentinian beef fat samples have somewhat higher hexachlorocyclohexane and dieldrin levels than UK-produced beef fat, but lower levels of DDT-derived residues. Normally, negligible hexachlorobenzene levels are noted, while polychlorobiphenyl traces are er-

ratic and very low. Limited surveys have also been made of other pesticide residues, including demeton-methyl, dimethoate, malathion, aldrin, bromide, and triphenyltin. Studies of toxic metals have noted an average dietary intake of 5-10 µg of mercury/day, largely determined by the fish component of the diet. The cadmium concentration of the average diet has been found to be 0.1-0.2 mg/wk; primary cadmium sources are brown body crab meat and crops grown near metal refineries. A survey of lead indicates its wider distribution in foods and higher residue levels; the daily total dietary lead intake is estimated at 0.2 mg/person (0.13 mg/kg), although canned baby food contains 0.24 mg/kg. Studies are proposed for the estimation of dietary copper, chromium, cobalt, zinc, and tin. Mycotoxin contamination is also discussed. No incidence patterns of nitrosamine presence are noted; however, cooking of protein food tends to be a source of greater secondary amines. Also, known environmental exposure levels for polynuclear aromatic hydrocarbons are relatively low, compared with those found in certain industrial atmospheres. (49 references).

5433 VINYL CHLORIDE POLYMERS IN CONTACT WITH FOOD. (Eng.) Schmidt, A. M. (No affiliation given). *Fed. Regist.* 40(171):40529-40537; 1975.

Proposed regulations restricting the uses of vinyl chloride (VC) polymers in contact with food, as suggested by the Food and Drug Administration, are reviewed. In general, the proposal permits the continued use of VC polymers in food packaging when the migration potential of VC is diminished, includes an interim regulation for the use of water pipes made from VC polymers, and prohibits all other use of VC polymers in food-contact articles. The chemical structure and properties of VC and VC homopolymers and copolymers are described. Earlier studies have indicated that polyvinyl chloride (PVC) is insoluble in various solvent systems used to simulate food. However, later migration studies have revealed residual VC from PVC bottles in distilled spirits and wines. No animal feeding studies have established a safe level of consumption when VC is extracted from containers into food. The existence of residual VC in articles made from VC polymers has been found to be related to the manufacturing process and the physical structure of the polymers; a model explaining the VC migration phenomenon is presented. Viewed as a simple diffusion phenomenon, experimental data indicate that while no VC is extractable from packaging materials, the greatest likelihood for migration of VC appears to be from PVC articles intended for one-time use. However, there is little likelihood that residual VC from PVC water pipes will become a component of potable water. Considerable data exist concerning the toxic effects of VC from atmospheric exposures, especially by inhalation and occupational contact; it is also suggested that VC is carcinogenic when ingested. Although a variety of uses of VC polymers in food-contact articles was previously approved, it is now suggested that widespread use be prohibited. It is concluded that no migration of VC from thin plas-

ticized film is expected, nor is any migration expected from jar and bottle cap liners and gaskets. No residual VC is reported in beer and soft drink can linings, but VC polymers used as coatings for fresh citrus fruits present the possibility of ingestion. Data also indicate that rigid and semi-rigid PVC articles intended to contact food may transmit VC to the food they contact. Proposed federal regulations and amendments are presented. (No references)

5434 ASBESTOSIS: A REASSESSMENT OF THE OVERALL PROBLEM. (Eng.) Haley, T. J. (Nat'l. Center for Toxicological Res., Jefferson, Ark. 72079). *J. Pharm. Sci.* 64(9):1435-1449; 1975.

The chemistry, industrial hygiene, animal and human toxicology, and carcinogenic aspects of the asbestosis problem are reviewed. Use of the generic term "asbestos" includes the varieties actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite. Various asbestos fiber types are analytically identified *via* polarizing microscopy, transmission electron microscopy, selected area electron diffraction, X-ray diffraction, IR spectrophotometry, atomic absorption spectrophotometry, and neutron activation analysis; electron beam instruments are the best for identification of asbestos fibers in tissue. Various biochemical, histological, and histochemical aspects are described. Industrial dust measurements are accomplished by use of an impringer, Owens jet counter, konimeter, thermal precipitator, or a membrane filter; protective procedures include use of enclosed working areas, general room ventilation, water spraying, local exhaust systems, and respiratory equipment. Animal toxicology experiments, employing i.p., intratracheal, intrapleural, and inhalation administration of all forms of asbestos, note numerous accounts of tumorigenesis; these include abdominal granulomas, pulmonary carcinomas, sarcomas, premesotheliomas, mesotheliomas, reticulosis, cuboidal epithelial metaplasias, and undifferentiated lung carcinomas. Tissue culture studies also reveal various aspects of cell toxicity. Considerations of human toxicology note the clinical signs, diagnostic procedures, and pathological changes of asbestosis. The significance of asbestos bodies in the pulmonary system is discussed, while epidemiological studies illustrate the long latent period, uncertain prior exposure level, and increased neoplasia attributed to asbestos. Unsuspected exposure to asbestos fibers *via* mining, asbestos friction materials, asbestos house insulation, pipe insulation, textile production, and various nonoccupational routes is discussed and evaluated. (246 references).

5435 ROW OVER IRRADIATION OF WHEAT. (Eng.) Sehgal, N. K. (Jullundur, India). *Nature* 257(5527):440; 1975.

The safety of radiation disinfected and preserved foods is debated. Indications that irradiated wheat could be hazardous to health are derived from numerous studies. Consumption of irradiated wheat

by animals and humans caused the development of polyploidy. Animals fed irradiated wheat transmitted chromosomal abnormalities to their offspring, and experienced faster mutations and reduced reproductive cells. However, other feeding trials with laboratory animals declare a variety of irradiated foods safe and wholesome for human consumption. Other studies on rats, mice, and monkeys have shown a 4-10-fold increase in polyploid cells of animals fed irradiated wheat, while the precise significance of such increased polyploidy remains uncertain. The production of aflatoxins has been found to be considerably greater in stored, irradiated wheat and potatoes; rotting is also accelerated. In view of continuing charges and arguments, no conclusions about the safety of irradiated foods for human consumption can yet be made. (No references)

- 5436 ON THE DISCRETENESS OF THE PHASES OF THE CELL CYCLE. (Eng.) Shackney, S. E. (Nat'l. Cancer Inst., Bethesda, Md. 20014). *J. Nat'l. Cancer Inst.* 55(4):827-829; 1975.

In populations (e.g. sarcoma 180) in which the rate of DNA synthesis increases and falls gradually, one can no longer speak of discrete cycle phases. The distinction between continuous and discrete models of cell cycles depends on the demonstration of the presence or absence of a discontinuity in the DNA content as a function of cell age. Factors which might obscure a discontinuity are discussed. Computer simulations reveal kinetic differences between leukemia and melanoma which correspond with their clinical behavior. The continuous model is useful in the analysis of human tumor cell behavior. (23 references)

- 5437 RADIOACTIVE CONTAMINATION OF THE ENVIRONMENT AND THE POSSIBLE CONSEQUENCES. (Eng.) Knizhnikov, V. A. (Biophysics Inst. of the U.S.S.R. Ministry of Health, Moscow, U.S.S.R.); Barkhudarov, R. M. *At. Energy Rev.* 13(2):171-214; 1975.

The main sources, pathways, doses, and consequences of radioactive environmental contamination are reviewed. The global nature of effects on the biosphere is discussed, and the sources of radioactive contamination are discerned. Three major sources are: radioactive fall-out following nuclear explosions, nuclear power stations and industries, and diagnostic radiology and radiotherapy. These are discussed in relation to nuclear weapons tests, nuclear explosions for peaceful purposes, nuclear-powered transport, and the problems of burial and safe handling of radioactive waste. Current levels of radioactive contamination of the biosphere are evaluated; the radiobiological significance is determined by: (1) the yield from fission or fusion of nuclear fuel, (2) the rate and level of uptake in food, (3) the rate of absorption from the gastrointestinal tract, (4) the extent of deposition in the critical organ, and (5) the type and energy of the radiation. The strontium-90 and cesium-137 con-

tent of soil and water has been evaluated, and the migration of the radioisotopes through biological chains has been investigated; particular attention has been given to isotopes in foodstuffs and in drinking water. While peaceful nuclear explosions and nuclear power stations constitute contamination pathways not connected with global fall-out, the major environmental contamination results from stratospheric fall-out. The effect of age and dietary habits on the accumulation of radioisotopes in the body is discussed. A consideration of the population doses from external and internal irradiation notes the various organ depositions of the isotopes, doses from the natural radiation background, and the medical therapeutic and diagnostic applications. The concepts of acceptable risk, somatic effects, genetic effects, and ecological aspects are discussed in relation to the possible consequences of radioisotope contamination of the biosphere. (185 references).

- 5438 ISOZYME PATTERNS OF BRANCHED-CHAIN AMINO ACID TRANSAMINASE DURING CELLULAR DIFFERENTIATION AND CARCINOGENESIS. (Eng.) Ichihara, A. (Sch. Medicine, Tokushima Univ., Tokushima, Japan). *Ann. NY Acad. Sci.* 259:347-354; 1975.

Isozyme patterns of branched-chain amino acid transaminase are reported for cellular differentiation and carcinogenesis and compared with findings on α -fetoprotein. The three isozymes can be separated by either DEAE cellulose column chromatography or acrylamide gel electrophoresis. Enzymes I and III are very similar in their substrate specificity, and their Km values are also similar. Enzyme II is specific for leucine, and its Km value is very high. Immunochemical studies on neutralization of the enzyme activities and Ouchterlony double diffusion tests suggest that the three forms are different proteins. Enzyme activity is very high in heart, kidney, and lactating mammary gland; liver, small intestine, and adipose tissue have low activity. Enzyme I has been found in all tissues examined; enzyme II has been found only in liver; and enzyme III was found to occur in brain, ovary, and placenta. Fetal liver contains only enzyme I; after birth, enzyme II appears and increases in activity. Enzyme III is not detectable in early fetal liver, and regenerating liver after partial hepatectomy retains the normal pattern of adult liver with enzymes I and II only. In a fast growing hepatoma, enzyme II was observed to be lost with the appearance of enzyme III, which has the same enzymological and immunochemical properties as enzyme III from normal brain. During induction of primary hepatomas by feeding rats with 3'-methyl-dimethylaminoazobenzene, a good correlation has been found between histological changes and changes in isozyme patterns: benign adenomas retained enzyme II without appearance of enzyme III, and all hepatomas except one showed the appearance of enzyme III with loss of enzyme II. When cultured rat hepatocytes were treated with 4-nitroquinoline oxide and dimethylaminoazobenzene, these cells transformed and showed tumorigenicity on transplantation in rats. Cells isolated from the tumors contained enzyme III, whereas untreated cells did not. Spontaneously

transformed cells that were not back-transplanted also acquired enzyme III, suggesting that expression of enzyme III by transformed cells is due to a change of gene expression. This theory is supported by the fact that the appearance of enzyme III is accompanied by chromosomal deviation. (35 references)

5439 EARTHWATCH: GUIDELINES FOR IMPLEMENTING THIS GLOBAL ENVIRONMENTAL ASSESSMENT PROGRAM ARE PRESENTED. (Eng.) Jensen, C. E. (4419 S.E. 20th Place, Cape Coral, Fla. 33904); Brown, D. W.; Mirabito, J. A. *Science* 190(4213):432-438; 1975.

The designation Earthwatch is adopted for the environmental assessment part of the United Nations Environmental Program (UNEP), which would provide the basis for responsible environmental management. Earthwatch is designed as a four part program involving monitoring, research, evaluation, and information exchange. Seven priority program areas that address critical global environmental needs are: 1) human settlements and habitat, 2) health of people and of the environment, 3) terrestrial ecosystems, 4) environment and development, 5) oceans, 6) energy, and 7) natural disasters. The Earthwatch program is subdivided, each area pertaining to a specific job. The aid of outside agencies is also welcome. Some of these new organizations and programs are: the Global Environmental Monitoring System, the International Referral System, the World Health Organization, the World Weather Watch, the Integrated Global Ocean Station System, the Geooperational Environmental Satellite, the Man and Biosphere program, the Food and Agricultural Organization, the International Hygrological program, the International Atomic Energy Agency, The International Councils of Scientific Unions, the Global Telecommunications System, and the Global Atmospheric Research Program. A fundamental concern when implementing comprehensive monitoring, research and evaluations programs is the proper management of data and information to ensure its availability both currently and in the future for analyses and the preparation of environmental assessments. (22 references)

5440 THE HAZARDS OF ASBESTOS. (Dut.) Plan- teydt, H. T. (No affiliation given). *Chem. Tech. (Amsterdam)* 30(3):A84-A89; 1975. (9 references)

5441 HORMONES IN COSMETICS--BENEFIT OR DANGER? (Eng.) Anonymous. *Manuf. Chem. Aerosol News* 46(4):23, 25, 27; 1975. (29 references)

5442 A BIBLIOGRAPHY ON THE TOXICOLOGY OF VINYL CHLORIDE AND POLYVINYL CHLORIDE. (Eng.) Heilmann, H. (Mt. Sinai Sch. Med., City Univ. New York, N.Y.); Lilis, R.; Hawkins, D. T. *Ann. N.Y. Acad. Sci.* 246:322; 1975. (389 references)

5443 POTT AND THE PROSPECTS FOR PREVENTION. (Eng.) Doll, R. (Univ. Oxford, England). *Br. J. Cancer* 32(2):263-272; 1975. (65 references)

5444 IONIZING RADIATION EXPERIMENTAL; RADIATION CARCINOGENESIS *IN VITRO*. (Eng.) Klein, J. C. (Radiobiological Inst., TNO, Rijswijk (Z. H.), The Netherlands). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 125-130. (30 references)

5445 THE ROLE OF VIRUS IN EVOLUTION. (Fre.) Christen, Y. (No affiliation given). *Recherche* 6(54):270-271; 1975. (2 references)

5446 CANCER OF THE CERVIX UTERI AND VENEREAL DISEASES. (Fre.) Lê, M. (I.N.S.E.R.M.); Lecharpentier, D.; Wolff, J.-P. *Concours Med.* 97(2):213-217; 1975. (No references)

5447 EMBRYONAL DEVELOPMENT, RETROGENESIS, AND CANCER. (Eng.) Anderson, N. G. (No affiliation given). *Akad. Wiss. Lit. Mainz Math. Naturwiss. Kl. Karl-August-Forster-Lect.* 11:7-44; 1975. (62 references)

5448 *IN VITRO* ASSAYS OF CELL-MEDIATED IMMUNITY TO HUMAN SOLID TUMORS: PROBLEMS OF QUANTIFICATION, SPECIFICITY, AND INTERPRETATION. (Eng.) Baldwin, R. W. (Cancer Res. Campaign Lab., The University, University Park, Nottingham NG7 2RD, England). *J. Natl. Cancer Inst.* 55(4):745-748; 1975. (39 references)

5449 GROWTH REGULATION THEORIES AND CHALONE CONCEPT: A REVIEW. (Eng.) Attallah, A. M. (Child. Hosp. Natl. Med. Cent., Washington, D.C.). *Clin. Proc. Child. Hosp. Natl. Med. Cent.* 31(6):108-113; 1975. (28 references)

5450 IMMUNOLOGICAL FACTORS IN THE GENESIS AND DEVELOPMENT OF NEOPLASTIC DISEASES. PART I. (Pol.) Steffen, J. (Instytut Onkologii 02-034 Warszawa, ul. Wawelska 15, Poland). *Nowotwory* 25(2):123-133; 1975. (95 references)

5451 THE HISTOCOMPATIBILITY-LINKED IMMUNE RESPONSE GENES. (Eng.) Benacerraf, B. (Harvard Medical Sch., Boston, Mass.); Katz, D. H. *Adv. Cancer Res.* 21:121-173; 1975. (101 references)

5452 MEMBRANE CELL MARKERS IN HUMAN LEUKAEMIAS AND LYMPHOMAS. (Eng.) Seligmann, M. (INSERM U 108, Res. Inst. Blood Diseases, Hopital Saint-Louis, 75475 Paris 10°, France). *Br. J. Haematol.* 31(Suppl.):1-4; 1975. (3 references)

- 5453 LEUKEMIA (A BIBLIOGRAPHY WITH ABSTRACTS). (Eng.) Harrison, E. A. (National Technical Information Service, Springfield, Va.) 139 pp., 1975. [available through National Technical Information Services, Washington, D.C. Document No. NTIS/PS-75/339/2GA]
- 5454 PREGNANCY-CONDITIONED TROPHOBLASTIC TUMORS. COURSE, PROGNOSIS AND THERAPY. (Ger.) Bruntzsch, U. (Innere Universitätsklinik und Poliklinik (Tumorforschung), Gesamthochschule Essen, West Germany); Gallmeier, W. M.; Schmidt, C. G. *Dtsch. Med. Wochenschr.* 100(7):313-318; 1975. (59 references)
- 5455 GENERAL DISCUSSION: ETIOLOGY AND PREVENTION OF PROSTATIC CANCER. (Eng.) Winkelstein, W. (P. W. Hutchins, Cancer Chemotherapy Reports, Natl. Cancer Inst., Blair Bldg., Rm. 3A05, Silver Spring, Md. 20910); Byar, D.; DeWys, W.; Shain, S.; Rapp, F.; Rosenthal, H.; *et al.* *Cancer Chemother. Rep. (Part 1)* 59(1):73-87; 1975. (12 references)
- 5456 LEUKEMIA-LYMPHOMA. CHEMICAL AND FAMILIAL FACTORS. (Eng.) Berger, R. (Centre Recherches Biologiques Neonatales, Hopital Port-Royal, Paris 14, France). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 222-227. (138 references)
- 5457 CLUSTERS OF LEUKEMIA-LYMPHOMA CASES: ANY ETIOLOGICAL SIGNIFICANCE? (Eng.) Pike, M. C. (Univ. Southern California Sch. Medicine, Los Angeles, Calif. 90033); Dworsky, R.; Smith, P. G. *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 244-247. (25 references)
- 5458 ENVIRONMENTAL FACTORS IN BREAST CANCER: THE EPIDEMIOLOGIC EVIDENCE. (Eng.) Cole, P. (Harvard Sch. Public Health, Boston, Mass.) *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 289-293. (26 references)
- 5459 EXPERIMENTAL CARCINOGENESIS TESTING FOR OCCUPATIONAL EXPOSURES. (Eng.) Safiotti, U. (Natl. Cancer Inst., Bethesda, Md. 20014). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 81-84. (7 references)
- 5460 NUTRITION 13: FIBRE. (Eng.) Heywood, P. F. (Sch. Public Health and Tropical Medicine, Univ. Sydney, N.S.W. 2006 Australia). *Med. J. Aust.* 2(5):179-182; 1975. (8 references)

CHEMICAL CARCINOGENESIS

- 5461 STUDIES ON THE RECOVERY OF AFLATOXIN B₁ INJECTED INTO FROZEN BEEF AT DIFFERENT INTERVALS OF STORAGE. (Eng.) Murthy, T. R. K. (Station de Biochimie et Physico-chimie des Cereales de l'I.N.R.A., Paris, France); Jemmali, M.; Rosset, R. *Z. Lebensm. Unters. Forsch.* 158(1):5-7; 1975.

The extraction, purification, and determination of aflatoxins in meat were studied. Beef (50g portions) was stored at 18 C for 20, 25, 32, 153, and 183 days. Frozen beef was thawed at room temperature, and about 2 µg aflatoxin B₁ in 2 ml acetone was injected. Aflatoxins were extracted with methanol 45 min later, transferred to chloroform, and purified by silica gel column chromatography. The samples showed a diminution in the recovery of injected aflatoxin B₁ with increasing storage periods. Aflatoxin B₁ was eluted from the silica gel column by chloroform-methanol; a blue fluorescent aflatoxin-like substance was eluted by ether. This latter substance was found only in stored frozen beef.

- 5462 INFLUENCE OF CARBON TETRACHLORIDE OR RIBOFLAVIN ON LIVER CARCINOGENESIS WITH A SINGLE DOSE OF AFLATOXIN B₁. (Eng.) Scotto, J. M. (Unite 9 de l-Institut National de la Sante et de la Recherche Medicale, Paris, France); Stralin, H. G.; Lageron, A.; Lemonnier, F. J. *Br. J. Exp. Pathol.* 56(2):133-138; 1975.

The effect of carbon tetrachloride on liver carcinogenesis induced by aflatoxin B₁ was studied in the rat. One hundred and thirty-six female Wistar rats were placed in one of the following groups: (1) 21 controls, (2) 21 treated with a single dose of aflatoxin B₁ (7 mg/kg) by stomach tube, (3) 28 intoxicated with CCl₄ (200 inhaled doses), (4) 26 intoxicated with aflatoxin followed by CCl₄, (5) 20 overloaded with riboflavin (25 parts/10⁶ in drinking water), (6) 20 overloaded with riboflavin and aflatoxin B₁. Slices of liver were removed either by autopsy during laparotomy, or during autopsy, and prepared for light microscopy. The frequency of hepatomas was almost equal in the aflatoxin group (9 of 21) and the aflatoxin-CCl₄ group (10 of 17). It was lower in the riboflavin-aflatoxin group (5 of 20). In these three groups, cirrhosis was never present in hepatomas. Megalocytosis was the first lesion observed. All tumoral livers had previous or concomitant megalocytosis. This modification was about as frequent, intense, and widespread in aflatoxin-CCl₄ and aflatoxin groups but appeared much earlier, as did the first hepatoma, in the aflatoxin-CCl₄ group. It was less frequent, less intense and less widespread in the riboflavin-aflatoxin group than in the aflatoxin group. There was also a lower frequency of hepatomas in the riboflavin-aflatoxin group, but the difference was not significant due to the small number of animals involved. A slight megalocytosis was observed in the riboflavin group not affected by the neoplastic process. The results suggest that the potential tumor cells are located among the megalocytic cells, without admitting that every megalocyte is obligatorily a precancerous cell. CCl₄ seems to act in shortening the time of appearance of megalocytosis. The protective effect of riboflavin should be regarded with more caution.

- 5463 CARCINOGENIC AND COCARCINOGENIC EFFECTS OF INHALED SYNTHETIC SMOG AND FERRIC OXIDE PARTICLES. (Eng.) Nettesheim, P. (Biol. Div., Oak Ridge Natl. Lab., Tenn.); Creasia, D. A.; Mitchell, T. J. *J. Natl. Cancer Inst.* 55(1):159-169; 1975.

The carcinogenic and cocarcinogenic activity of synthetic smog, ferric oxide (Fe₂O₃) dust, and a mixture of the two, was determined in a long-term inhalation study using male Syrian hamsters. Inhaled Fe₂O₃ particles increased diethylnitrosamine (DEN, 0.25 mg/wk, sc for 12 wk) tumorigenicity from 10% to 20% observed incidence, in the peripheral lung. Synthetic smog (gasoline evaporated into O₂ and O₃) did not. At 40 ppm methane equivalents or 40 mg/m³, respectively, neither air pollutant by itself appeared carcinogenic. Fe₂O₃ caused pulmonary fibrosis and synthetic smog caused alveolar bronchiolization in many of the exposed animals. No respiratory tract tumors were observed in hamsters not given DEN.

- 5464 PHENOLS IN SMOKED, CURED MEATS: NITROSATION OF PHENOLS IN LIQUID SMOKES AND IN SMOKED BACON. (Eng.) Knowles, M. E. (Ministry of Agriculture, Fisheries and Food, Food Science Div., Colney Lane, Norwich NR4 7UA, U. K.); Gilbert, J.; McWeeny, D. J. *J. Sci. Food Agric.* 26(3):267-276; 1975.

The products formed on nitrosation of a liquid smoke emulsion have been identified and nitrogen-containing compounds were determined in exclusively phenol-containing extracts from bacon which were absent in similar unsmoked bacon controls. Nitrosations were carried out on the phenols in a smoke condensate and commercial 2-methoxy-4-methylphenol, each in the form of a casein emulsion. An 8:1 casein-phenol emulsion was prepared. The volume was brought to 120 ml with water, the pH adjusted to 2.0 with 1 N HCl and sodium nitrite (0.2 g) was added (the nitrosation of the smoke condensate was carried out using 1.0 g sodium nitrite). The reactants were stirred for 2 hr. In bacons produced by three techniques (traditional, liquid smoke dipping, and liquid smoke spraying) analyses were carried out on the following: raw bacon, fried bacon, volatiles collected from fried bacon, and fried bacon after simulated digestion. Extracts of nitrosated phenols and bacon were analyzed by gas chromatography. Major products identified in extracts of nitrosated liquid smoke included 2-nitro-5-methylphenol, 2-nitro-4,6-dimethylphenol, 2-nitro-4-ethylphenol, and 2-methoxy-4-nitrophenol. The raw smoked bacon contained 12 nitrogen-containing peaks not present in unsmoked bacon, indicating that either (1) reaction of nitrite with phenols occurs in the meat matrix; or (2) nitrosation occurs in the curing pickle and the products are absorbed by the meat; or (3) both of these reactions occur. The effect of frying was to produce two new nitrogen-containing peaks in addition to retaining most of those in the raw bacon. The results for commercially sprayed smoked bacon indicate that one of the peaks in the fried bacon extract corresponded to 2-nitro-5-methylphenol and another to 2-methoxy-6-nitrophenol. 2-Nitro-

5-methylphenol was identified in raw and fried traditionally smoked bacon. Another product was tentatively identified as 2-nitro-4,6-dimethylphenol. Two other peaks were tentatively identified as 2-nitro-4-*sec*-butylphenol, and 2-methoxy-4-methyl-6-nitrophenol. The nature of the products isolated suggests that the initial reaction is generally nitrosation, ortho to the phenolic hydroxyl. Although it was not possible to make quantitative comparisons of the nitrosation products in bacons produced by the different methods, it is concluded that some nitrosation occurs in bacons produced by the three techniques studied.

- 5465 CARCINOGEN AND SMOKE INDUCED EARLY ALTERATIONS IN THE SYRIAN GOLDEN HAMSTER RESPIRATORY EPITHELIUM AS REVEALED BY ELECTRON MICROSCOPY. (Eng.) Mohr, U. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Hannover, West Germany); Reznik-Schuller, H. *Oesterr. Z. Onkol.* 2(2/3):68-72; 1975.

Experiments were conducted to elucidate the early steps of lung carcinogenesis and to clarify the mode of its subsequent developmental stages. Twelve-week-old Syrian golden hamsters were treated once weekly with 0.63 mg benzo(a)pyrene [B(a)P] administered intratracheally. Another group of hamsters was exposed once daily for one year to cigarette smoke by means of a smoking machine (Type Hamburg II). Trachea, lobar and segmental bronchi of the animals were examined with the electron microscope. The smoke-induced epithelial alterations resembled, in many aspects, those caused by ten weeks of B(a)P treatment. In the tracheal and bronchial epithelia of both B(a)P-treated and smoke-exposed animals, the ciliated cells often demonstrated huge cytoplasmic processes that contained groups of polyribosomes. In addition, the bronchial epithelial cells of both groups possessed numerous, large, multivesiculated bodies.

- 5466 REGENERATIVE RESPONSE OF THE RAT TRACHEAL EPITHELIUM AFTER ACUTE EXPOSURE TO TOBACCO SMOKE: A QUANTITATIVE STUDY. (Eng.) Wells, A. B. (Royal Cancer Hosp., Clifton Ave., Sutton, Surrey SM2 5PX, England); Lamerton, L. F. *J. Natl. Cancer Inst.* 55(4):887-891; 1975.

The regenerative response of the rat tracheobronchial epithelium after acute exposure to tobacco smoke was studied. Cigarettes were smoked automatically, and the smoke was diluted with air before being inhaled by male August rats. Twenty-four hours after the animals were subjected to tobacco smoke, and with vinblastine (2 mg/kg, ip, given six hours before sacrifice) as a metaphase-arrest agent, a wave of cell proliferation occurred. The intensity of the response was related to the type of smoke (it was more severe for cigarette than cigar tobacco) and depended on the concentration of smoke, but the timing of the response after moderate exposure was constant. The wave of proliferation would appear to be a local response to cell loss or damage,

though morphologically the observed changes were slight. With repeated daily exposure, some adaptation of the tissue was apparent, in that the wave of rapid cell reproduction did not recur, but this did not imply that there was no progression of effect with respect to other pathologic processes. The responses to tobacco smoke and sulfur dioxide (800 ppm, two hours) were compared; the response differed slightly from that for cigarette smoke, and a brief period of cell loss was evident. Cell proliferation provided a useful and rapid test of certain irritant effects of different types of tobacco smoke, but it was essential that animals free of chronic respiratory disease be used.

- 5467 PRELIMINARY STUDIES ON THE FATE OF INHALED VINYL CHLORIDE MONOMER (VCM) IN RATS. (Eng.) Hefner, R. E., Jr. (Health and Environmental Res., Dow Chemical U.S.A., Midland, Mich. 48640); Watanabe, P. G.; Gehring, P. J. *Environ. Health Perspect.* 11:85-95; 1975.

Male Sprague-Dawley rats were exposed to vinyl chloride monomer gas (VCM) in a closed recirculating system. The rate at which VCM was removed from the system *via* metabolism was determined for rats exposed to initial concentrations of VCM ranging from 50-1,167 ppm. Upon exposure to initial concentrations of 50-105 ppm, the rate of metabolism was $8.04 \pm 3.40 \times 10^{-3} \text{ min}^{-1}$. Upon exposure to initial concentrations ranging from 220 to 1,167 ppm, the rate constants were less; the mean value being $2.65 \pm 1.35 \times 10^{-3} \text{ min}^{-1}$. Regardless of concentration, the disappearance followed apparent first order kinetics. Pretreatment of rats with pyrazole (320 mg/kg) prior to exposure to 65 and 1,234 ppm VCM caused 71 and 87% reductions, respectively, in the rate of metabolism. Ethanol (5 ml/kg, 95%) caused 96% and 83% reductions in the rate of VCM metabolism by rats exposed to 56 and 97 ppm VCM, respectively. Ethanol was less effective in blocking the rate of metabolism by rats exposed to high concentrations of VCM; 46 and 36% in rats exposed to 1,025 and 1,034 ppm VCM. In rats exposed to 65 ppm VCM, SKF-525-A (75 mg/kg) administration caused no inhibition of the rate of VCM metabolism; however, a 19% inhibition was seen in rats exposed to 1,038 ppm. The nonprotein sulfhydryl content of the liver (glutathione and cysteine) of rats exposed to 50-15,000 ppm VCM was reduced without a relationship to dose. With repeated daily exposure, the degree of reduction was reduced. Preliminary results indicate that the primary metabolites of VCM react with the non-protein sulfhydryl. Final metabolic products excreted in the urine appeared to be *S*-(2-hydroxyethyl)cysteine and *S*-(2-carboxymethyl)cysteine and the respective *N*-acetyl derivatives. Monochloroacetic acid was identified as another potential metabolite. The results suggest that VCM is readily and extensively metabolized. Metabolism *via* the primary pathway, postulated to involve alcohol dehydrogenase, is swamped by exposures to concentrations exceeding 220 ppm. In rats exposed to concentrations at and exceeding this level, metabolism occurs *via* a secondary pathway(s), postulated to be epoxida-

tion and/or peroxidation. These results are considered pertinent in assessing the potential hazard at low-level exposures to VCM.

5468 EXPERIMENTAL CHRONIC POISONING WITH VINYL CHLORIDE (MONOCHLOROETHENE). (Eng.)
Prodan, L. (Inst. Med. Pharm., Cluj, Romania);
Suciu, I.; Pislaru, V.; Ilea, E.; Pascu, L. *Ann. N.Y. Acad. Sci.* 246:159-163; 1975.

The effects of long-term vinyl chloride exposure on guinea pigs were studied. The animals were exposed to 10% vinyl chloride in an inhalation chamber for two hours daily for 1-3 mo. In addition, some animals were given daily po doses of vitamin C (10 mg). Vinyl chloride exposure resulted in growth retardation, the extent of retardation increasing with increasing duration of exposure. Vitamin C significantly reduced the extent of growth retardation. Spontaneous motility was also reduced in the vinyl chloride-treated guinea pigs, while renal weight and the weight of the adrenal glands was significantly increased. Vitamin C alone also produced increases in adrenal gland weight. There were no significant hematological changes or variations in the vitamin C content of the adrenal glands. Vinyl chloride exposure resulted in intense hepatocellular lesions, moderate lesions of the renal glomeruli, marked lesions in the renal tubules, a strong cellular reaction in the spleen, and a marked fibrosis in the lungs. Vitamin C reduced the gravity of the vinyl chloride-induced lesions, and the lesions showed a certain degree of reversibility after shorter periods (1-2 mo) of vinyl chloride exposure.

5469 CHROMOSOMAL AND DOMINANT LETHAL EFFECTS OF VINYL CHLORIDE. [letter to editor]. (Eng.)
Purchase, I. F. H. (Central Toxicology Lab., Alderley Park, Nr. Macclesfield, Cheshire SK10 4TJ, England);
Richardson, C. R.; Anderson, D. *Lancet* 2(7931):410-411; 1975.

Chromosomal aberrations were studied in 80 workers, 56 of whom had been exposed to vinyl chloride monomer. Blood samples were taken and lymphocytes were cultured for 48 or 72 hr. All slides were coded before scoring, and 100 cells from each worker were analyzed. There was a significantly increased percentage of B, Cu, and Cs cells in 56 exposed workers as compared to the 24 nonexposed workers; this confirms previous reports and suggests that vinyl chloride has a detectable effect on chromosomal aberrations in man. A dominant lethal study was performed in mice to determine if any genetic effects could be induced in germ cells by vinyl chloride monomer. Fifteen male mice per treatment group were exposed to 30,000, 10,000, and 3,000 ppm vinyl chloride monomer for six hours a day on five consecutive days, and an examination for dominant lethal effects in two females mated with each male for eight consecutive weeks was carried out. There was no significant increase in the number of early deaths per implantation, indicating that vinyl chloride monomer does not produce dominant lethal mutations in mice. These results suggest that the mutagenic effects of vinyl chloride do not occur in

the germ cells; this is possibly because active metabolites of vinyl chloride are responsible for the toxic effects, and these do not reach the testis.

5470 INTESTINAL TUMORS OF RATS BY GASTRIC OR INTESTINAL ADMINISTRATION OF CYCAD EXTRACT AND CYCASIN. (Eng.) Watanabe, K. (Kagoshima Univ. Sch. Medicine, 1208-1 Usuki-cho, Kagoshima 890, Japan); Yoshii, H.; Iwashita, H.; Muta, K.; Hamada, Y.; Hamada, K.; Isaka, H.; Nishi, M. *Cann* 66(4): 449-453; 1975.

Target organs in cycasin carcinogenesis were studied. Sprague-Dawley rats were given one of the following treatments: gastric intubation of 3 ml/kg cycad extract ("group 1," ten females and 20 males); rectal infusion of 50 mg/kg cycasin once weekly for 12 wk ("group 2," 11 females, 23 males); or rectal infusion of 3 ml/kg cycad extract once weekly for 12 wk after external colostomy at 1/3 proximal portion of the large intestine ("group 3," 11 females, 20 males). The incidence for intestinal tumors for groups 1, 2, 3 were 95.8%, 84.2%, and 38.9%, respectively. In group 1, intestinal tumors developed in any portion of the intestinal tract ranging from the duodenum to the rectum. In group 2, tumors developed in the mucosa of the large intestine. In group 3, however, tumors arose from sites of the intestinal mucosa which were not in direct contact with the cycad extract infused. A possible hypothesis for production of tumors in the intestinal mucosa which was never in contact with the cycad extract (group 3): methylazoxymethanol or other cycad metabolites produced by intestinal flora may enter the circulating blood, be further metabolized by the liver, excreted into the bile, and thus cause intestinal tumors.

5471 ESTRIOL PREVENTION OF MAMMARY CARCINOMA INDUCED BY 7,12-DIMETHYLBENZANTHRACENE AND PROCARBAZINE. (Eng.) Lemon, H. M. (Univ. Nebraska Med. Cent., Omaha). *Cancer Res.* 35(5):1341-1353; 1975.

Seventeen estrogenic and nonestrogenic steroids were tested for their ability to inhibit mammary carcinomas induced in mature Sprague-Dawley female rats by po administration of 7,12-dimethylbenz(a)anthracene (DMBA, 20 mg) or procarbazine (PC, 50 mg). The steroids were incorporated at concentrations of 1-20% into NaCl pellets implanted sc 48 hr prior to carcinogen administration. A total of 105 steroid-implanted or untreated rats followed to death (234-256 days) developed no breast carcinomas. From 51-57% of 318 rats fed either of the carcinogens showed evidence of breast carcinoma after 136-156 days. Nonbreast carcinomas and sarcomas developed in 5-10% of the carcinogen-treated rats. Estriol administered as a 0.15-0.60 mg/pellet reimplanted every two months reduced breast carcinoma incidence to 5-7% in 106 rats given DMBA or PC. Estrone and 17 β -estradiol (0.50-1.14 mg) reduced breast tumor incidence in DMBA-treated rats to 22-5%, compared with 45-47% in carcinogen controls. At similar doses, estrone was significantly more inhibitory for PC-induced tumors.

Epiestriol also reduced breast cancer incidence to one-half that observed in carcinogen-treated rats. Possible inhibition of breast tumor development after PC feeding was noted with estrone 3-sulfate at 0.88 mg/pellet. Breast cancer incidence in 220 rats was not altered by treatment with D-Equilenin, 6-dehydroesterone, 16-keto-17 β -estradiol, 2-hydroxy-17 β -estradiol, 2-hydroxyestriol, estradiol-17 α , 16, 17-epiestriol, 17-epiestriol, testosterone, progesterone, corticosterone, dehydroepiandrosterone, or hexestrol. Castration prior to DMBA feeding markedly reduced breast tumor incidence in Sprague-Dawley females, and this low incidence was not altered by estriol, estrone, or 17 β -estradiol. The inhibition of DMBA- or PC-induced carcinogenesis in intact females by sustained low doses of estriol supports published data suggesting an inverse relationship between the renal excretion of estriol to estrone plus β -estradiol and risk of breast cancer in women. Based on the concentrations used in this study, 2.5-5.0 mg/day estriol, po, should be a suitable dose for use in clinical trials in postmenopausal cancer patients.

- 5472 EXPERIMENTAL INDUCTION OF PANCREATIC ADENOCARCINOMA IN RATS. (Eng.) Dissin, J. (Veterans Admin. Hosp., Forest Hills Div., Augusta, Ga. 30904); Mills, L. R.; Mains, D. L.; Black, O., Jr.; Webster*, P. D., III *J. Natl. Cancer Inst.* 55(4):857-864; 1975.

Adenocarcinomas of the pancreas were experimentally induced in male Sprague-Dawley rats after the implantation of 7,12-dimethylbenz[a]anthracene (DMBA). Rats were anesthetized with pentobarbital sodium, the pancreas was exposed, and a 2- to 3-mm incision was made in the "head" of the pancreas approximately 1 cm from the duodenum. Crystalline DMBA (2-3 mg) was implanted and the incision was closed with silk suture. Eighteen of 21 animals developed tumors in the pancreas from 119 to 363 days after implantation (mean, 194 days). Ten animals developed tumors in less than 180 days. The adenocarcinomas were invasive, metastasized, and had pronounced ductal cell characteristics. The light-microscopic morphology of these pancreatic tumors is presented. Most of the tumors had prominent desmoplastic stroma. DMBA implantation in the pancreas of the rat induces an adenocarcinoma resembling ductal carcinoma in humans.

- 5473 THE CHANGES IN RNA SYNTHESIS AT EARLY STAGES OF AMINOAZO CARCINOGENESIS. (Rus.) Mironov, N. M. (Inst. Experimental and Clinical Oncology, Acad. Medical Sciences, Moscow, U.S.S.R.); Adler, V. V.; Sokolov, N. A.; Zaboikin, M. M.; Shapot, V. S. *Biokhimiia* 40(4):861-868; 1975.

Changes in the RNA synthesis of isolated hepatocyte nuclei were studied in male Wistar rats after the introduction of a single 100, 300 or 500 mg/kg dose of 3'-methyl-4-dimethylaminoazobenzene (3'-MDAB) or of its noncarcinogenic analog 2-methyl-4-dimethylaminoazobenzene (2-MDAB) into the stomach. The hepatocyte nuclei were isolated 20-68 hr after

administration of the substances. Both substances caused an increase in RNA synthesis in the hepatocyte nuclei *in vitro*. The intensification of ribosomal RNA synthesis preceded the increase in Mn^{2+} , $(NH_4)_2SO_4$ -dependent RNA-polymerase activity. The activation of RNA synthesis was slightly more pronounced in the case of the carcinogenic substance. The differences in the RNA synthesis were not due to the effect of nuclease in the nuclei. The measurement of certain parameters of RNA synthesis suggests that the increase in synthesis by the hepatocyte nuclei (found *in vitro* at early stages of the action of 3'-MDAB) should be regarded as a manifestation of its toxic effect, and that it is due to an increase in the concentration of RNA-polymerase which is capable of catalyzing RNA synthesis in the nuclei. Since the increase in RNA synthesis was observed following the administration of both substances, the assumed toxic effect can not be related to the phenomenon of carcinogenesis.

- 5474 SECRETORY FUNCTION OF THE STOMACH IN PRETUMOR CONDITIONS AND TUMORS. (Rus.) Arkhipov, G. N. (Inst. of Nutrition of the USSR Acad. of Medical Sciences, Moscow, USSR); *Vopr. Onkol.* 21(6):49-54; 1975.

The effect of 3-methylcholanthrene deposits, introduced into the stomach in spherical polyethylene capsules, on the secretory function of the stomach was studied in 38 rats. The substance was mixed with medicinal vaseline at a rate of 5:95. Gastric tumors were found in 5 of the 19 surviving animals 13-17 mo after the introduction of 3-methylcholanthrene. The tumors ranged in size from 4 x 6 x 10 mm to 18 x 25 x 36 mm. Neither the carcinogenic substance, nor precancerous changes of the gastric mucosa caused any changes in the secretory function of the stomach. Shifts toward achylia (reduction in the specific volume of the gastric juice secreted, reduced acidity of the gastric juice, and reduced proteolytic activity) were observed first at a date when macroscopically manifest tumors were found. The changes in the gastric secretion toward achylia correlated with the size of the tumor. The findings indicate that the changes in the gastric secretion are due to the reduced surface area of the functional gastric mucosa as a result of the spread of the tumor. Similar changes in the gastric secretion, produced by diet, nerve stimulation, and drugs in earlier experiments, reduced the resistance of the stomach to the subsequent action of carcinogens, i.e., they predisposed the stomach for the tumor process.

- 5475 CELL PROLIFERATION AND SUBCELLULAR LOCALIZATION OF ALKALINE PHOSPHATASE ACTIVITY IN RAT LIVER PARENCHYMA DURING AZO DYE CARCINOGENESIS. (Eng.) Karasaki, S. (Institut du Cancer de Montreal, Montreal, Canada). *Cancer Res.* 35(3):482-491; 1975.

A combined method of phosphatase histochemistry and [3H]thymidine radioautography was devised to study the subcellular localization of alkaline phosphatase

tase (AP) activity with the changing pattern of cell proliferation in precancerous livers of Wistar rats fed 0.06% dimethylaminoazobenzene. After 50 hr of continuous infusion of [3 H]thymidine into the rats, labeled liver tissues were fixed in glutaraldehyde. Sections were incubated for AP activity in a lead citrate medium (pH 9.4) with β -glycerophosphate as substrate. Light and electron microscopic examinations of radioautographs revealed that focal groups of 3 H-labeled hepatocytes within hyperplastic nodules were coincident to hyperbasophilic foci and distinguishable from the surrounding parenchyma, which was sparsely labeled. Proliferative hepatocytes in the foci exhibited enzyme reaction product indicative of AP activity along the entire surface membranes. The surface AP topography was in contrast to that of the surrounding hyperplastic parenchyma, in which regenerative hepatocytes showed a normal localization of AP activity at the bile canalicular membranes. The L-phenylalanine-sensitive and heat-resistant activity of hyperbasophilic hepatocytes was different from that of normal hepatocytes. The surface enzyme differentiation was accompanied by a decrease of cytoplasmic AP. Golgi elements apparently function in the mobilization of AP into the surface membranes. The phenomena of AP alterations might be related to the abnormal control of cell proliferation and cyto-differentiation leading to malignant growth.

- 5476 STUDIES ON THE INDUCTION OF DAB METABOLIZING ENZYME ACTIVITY AND OTHER MICROSOMAL ENZYME ACTIVITY IN THE LIVER OF RATS FED COPPER. (Eng.) Yamane, Y. (Faculty Pharmaceutical Sciences, Chiba Univ., 1-33 Yayoi, Chiba, 280, Japan); Sakai, K. *Chem. Pharm. Bull.* 23(7):1440-1445; 1975.

The role of copper in enhancing the activities of 4-dimethylaminoazobenzene (DAB) metabolizing enzymes in rat liver was studied in female Wistar rats fed a diet containing 0.5% basic cupric acetate or 0.06% 3'-methyl-DAB (3'-Me-DAB) for four weeks. In some experiments, microsomes from control rats were used to determine the *in vitro* effects of Cu, flavin adenine dinucleotide (FAD), or β -diethylaminoethyl-diphenyl-propylacetate \cdot HCl (SKF-525A) on enzyme activity. Added Cu did not stimulate *in vitro* microsomal DAB azo reductase activity at concentrations from 1-100 μ M; at 50 and 100 μ M, Cu decreased enzyme activity. FAD inhibited azo reductase activity at 10^{-3} but caused a slight increase in activity at concentrations of 10^{-6} or 10^{-5} M. In copper-fed rats, increases in the copper and riboflavin contents of liver microsomes were correlated with increases in DAB azo reductase and ring hydroxylase levels in the microsomes. SKF-525A (2×10^{-4} M) strongly inhibited ring hydroxylase activity in microsomes from both control and copper-treated rats but had no significant effect on N-demethylase or azo reductase activity. Microsomal NADPH cytochrome c reductase activity increased in parallel with azo reductase activity in rats fed copper, while in 3'-Me-DAB-treated rats the activity of the former enzyme increased and that of the second decreased. Concurrent administration of copper and 3'-Me-DAB had an

additive effect on NADPH cytochrome c reductase activity and a competitive effect on azo reductase activity. The increase in DAB ring hydroxylase activity in microsomes from copper-fed rats was paralleled by an increase in microsomal cytochrome P-450 content. It is concluded that the enhancement of DAB metabolizing enzyme activities in livers of rats fed copper cannot be ascribed solely to an increase in the copper content of liver microsomes. The suppressive effect of copper on liver carcinogenesis by 3'-Me-DAB may be attributable to the effect of the latter on DAB reductase activity.

- 5477 A STUDY OF α_1 -FETOPROTEIN LEVELS DURING EXPOSURE TO 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE AND ITS ANALOGS. (Eng.) Becker, F. F. (New York Univ. Sch. Med., N. Y.); Horland, A. A.; Shurgin, A.; Sell, S. *Cancer Res.* 35(6):1510-1513; 1975.

Serum α -fetoprotein (AFP) levels were determined in male SD rats exposed to the hepatocarcinogen 3'-methyl-4-dimethylaminoazobenzene (MDAB). MDAB was added to riboflavin-free diets and to normal diets at the levels of 0.00125%, 0.0055%, 0.012% and 0.06%. Blood samples and livers were taken each wk for six wk. The histology of the livers at the 0.06% level revealed a progressive central hyaline degeneration of hepatocytes followed by death and clearance of cellular fragments. During the first three wk the involvement was zonal, and nodular aggregates of hepatocytes occurred by the fourth wk. The effect was dose-dependent and very mild in the normal diet. The mitotic indices of hepatocytes following exposure to 0.06% MDAB were highest after the first two wk, after which the level dropped to a rough plateau. Analogs of the carcinogen, 2-methyl-4-dimethylaminoazobenzene or *p*-aminoazobenzene, produced few histologic or mitotic changes. AFP levels increased continuously upon MDAB treatment, rising from 179 ng/ml at two wk to 2,900 ng/ml after six wk. Carcinogen treatment with a normal diet produced smaller increases. An all-or-none effect was achieved at the lower doses, with 0.012% giving a minimal response. Analogs of MDAB had no effect on AFP levels. Hepatectomized rats treated with carcinogen showed a constant drop in serum AFP levels with time. The results indicate that serum AFP levels can be stimulated with MDAB. This stimulation occurs almost immediately and to greater levels than with many malignant hepatocellular carcinomas.

- 5478 COMPARATIVE EFFECT OF PHENOBARBITAL AND 3-METHYLCHOLANTHRENE ON AZODYE METABOLISM IN RAT LIVER. I. *IN VITRO* STUDIES ON DETOXICATION AND ACTIVATION PROCESSES. (Eng.) Decloitre, F. (Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94800-Villejuif, France); Martin, M.; Chauveau, J. *Chem Biol Interact* 10(4):229-238; 1975.

The effect of phenobarbital (PB) and 3-methylcholanthrene (3-MC) administration on detoxication and activation of 4-dimethylaminoazobenzene (DAB) was

studied in rat liver microsomes. Azoreductase activity and *in vitro* DAB metabolite binding to calf thymus DNA and microsomal protein were simultaneously determined. Pretreatment of rats with 3 daily injections of PB (80 mg/kg) did not significantly modify azoreductase activity but increased DAB metabolite binding to DNA (+67%) and to protein (+123%). When 3-MC was given ip, (20 mg/kg) azoreductase was not modified and DAB metabolite binding to DNA and to protein was enhanced eight-fold. After administration of 3-MC in the diet (3.9 mg/kg/day, 11 days) azoreductase activity was decreased (-40%), DAB metabolite binding to DNA was unchanged and DAB metabolite binding to protein tripled. Thus the balance between the formation of DAB metabolites bound to DNA and azoreduction led to an increased activation/reduction ratio only by 3-MC injection. In every case, the formation of DAB metabolites bound to protein was significantly increased as compared with detoxication. Different effects of PB and 3-MC are discussed with reference to the synthesis of distinct cytochromes.

- 5479 COMPARATIVE ENHANCING EFFECTS OF PHENOBARBITAL, AMOBARBITAL, DIPHENYLHYDANTOIN, AND DICHLORODIPHENYLTRICHLOROETHANE ON 2-ACETYLAMINOFLUORENE-INDUCED HEPATIC TUMORIGENESIS IN THE RAT. (Eng.) Peraino, C. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, Ill. 60439); Fry, R. J. M.; Staffeldt, E.; Christopher, J. P. *Cancer Res.* 35(10):2884-2890; 1975.

Earlier studies showed that phenobarbital feeding enhanced hepatic tumorigenesis in rats previously fed 2-acetylaminofluorene for a brief period. As part of an investigation of the mechanism of this enhancement, the present study evaluated the relative enhancing abilities of amobarbital, diphenylhydantoin, and dichlorodiphenyltrichloroethane (DDT), agents that resemble phenobarbital to varying degrees in their effects on liver structure and metabolism. A comparison of hepatic tumor yields in Sprague-Dawley rats fed 0.02% 2-acetylaminofluorene for 18 days, followed by the test substance for 389 days (sequential treatment), showed that amobarbital and diphenylhydantoin had no enhancing activity, whereas the enhancing effect of DDT was similar to that of phenobarbital. The dietary concentration of each test agent was 0.05%. These results show that the sequential treatment technique readily distinguishes among substances differing in enhancing ability and should prove useful in screening additional substances for this activity. The comparative biochemical effects of these substances in the liver can then be correlated with their relative enhancing abilities to provide information on the molecular events specifically associated with enhancement. Such correlations were initiated in this study by comparing the acute effects of four test substances each given ip on liver weight and DNA synthesis. Phenobarbital (83 mg/kg) and DDT (112 mg/kg) each increased liver DNA synthesis and liver weight. Amobarbital (75 mg/kg) and diphenylhydantoin (44 mg/kg) suppressed DNA synthesis but had no marked effect on liver weight. Phenobarbital and DDT both increased the early tumor incidence rate and maintained an increment in tumor inci-

dence over that in the other treatment groups throughout the experiment, although it is not clear whether this increment would persist indefinitely. In addition, although the spectrum of tumor types observed ranged from highly differentiated to poorly differentiated in all treatment groups, DDT and phenobarbital selectively increased the incidence of highly differentiated tumors throughout most of the experiment. DDT might appropriately be classified with phenobarbital as an enhancer of tumorigenesis.

- 5480 ON THE INFLUENCE OF CHLORAMPHENICOL ON THE INDUCTION OF LUNG ADENOMAS BY URETHANE IN MICE. (Eng.) Shabad, L. M. (Inst. Experimental and Clinical Oncology, Acad. Medical Sciences, 115 478 Moscow, U.S.S.R.); Bogush, T. A.; Belitsky, G. A. *Neoplasma* 22(4):347-354; 1975.

The effect of chloramphenicol on the induction of lung adenomas by sc urethane in male and female A- or BALB/c mice was investigated. Four experimental schemes were used: (1) 1 mg urethane/day for 4-5 days three hours after chloramphenicol (total dose of urethane 4 mg/g, of chloramphenicol, 4 mg/g); (2) 1 mg/g urethane once three hr after chloramphenicol; (3) chloramphenicol only for three days, on days 4, 6, 8 and 10, chloramphenicol with urethane (0.25 mg/g two hours after chloramphenicol) on days 5, 7, 9, 11 and 12 chloramphenicol (total dose of urethane 1 mg/g, of chloramphenicol, 12 mg/g); and (4) chloramphenicol only for three days, chloramphenicol on days 4, 5 and 6 two hours prior to 0.25 mg/g urethane and four hours afterward, and chloramphenicol on days 7 and 8 (total dose of urethane 0.75 mg/g, of chloramphenicol, 11 mg/g). The experimental animals (440) were given a standard diet and killed in 3-4 mo. The lungs were fixed in formalin and macroscopically visible tumor nodules counted. Material from experiments 1 and 4 was examined histologically. Histological preparations were made either from macroscopically visible lung adenoma (experiment 1) or from the whole upper part of the right lung (experiment 4). When the wt ratio between the concentrations of urethane and chloramphenicol was 1:1, chloramphenicol had no influence on the blastomogenic action of urethane. When the dose of urethane was reduced and the wt ratio between urethane and chloramphenicol was maintained at 1:1, there was a decrease in the number of adenomas/mouse and in the total number of adenomas/group. Approximately the same protective effect of chloramphenicol was obtained in experiments on group 4. Under the conditions of group 4, chloramphenicol was not able to change the percentage of mice with adenomas; notwithstanding its administration, adenomas developed in 80% of the mice. In all the experiments, chloramphenicol preferentially inhibited the development of large and medium-sized adenomas. Diffuse hyperplasia was observed less frequently in the animals in experiment 1 which received urethane and chloramphenicol (3/16) than in those which received urethane only (10/16). In experiment 4, lung preparations from unprotected mice (87) showed twice as many adenomas as those from mice protected with chloramphenicol (74). Two possibilities are suggested to explain the mechanism of the protec-

tive action of chloramphenicol in urethane-induced adenomogenesis in the mouse lung: (1) influence on enzyme systems and (2) binding with cell macromolecules.

- 5481 CELL-CYCLE VARIATIONS IN ONCOGENIC TRANSFORMATION IN SYNCHRONIZED MOUSE EMBRYO CELLS IN CULTURE. (Eng.) Bertram, J. S. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, Wis.); Heidelberger, C. *Cell Cycle in Malign. Immun., Proc. Annu. Hanford Biol. Symp.*, 13th. Richland, Washington, U. S. Energy Research and Development Administration, 1975, pp. 359-368.

Malignant transformation was induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG, 4 µg/ml) in the C3H/10T1/2 CL8 line of mouse-embryo fibroblasts synchronized by amino acid deficiency. Treatment of cells at various times after release from arginine or isoleucine deficiency or from postconfluence inhibition of cell division resulted in a maximum transformation frequency in cells treated between four hours prior to S phase and the G₁/S boundary. No differences were detected in either the rate of binding of tritiated MNNG to logarithmic phase cells in comparison to cells blocked in G₁ of the cycle or in the extent and stability with time of binding to cells in the sensitive and insensitive phases of the cell cycle.

- 5482 INACTIVATION OF MAMMALIAN DNA METHYLASE ACTIVITIES BY *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE. (Eng.) Drahovsky, D. (Abteilung für Therapeutische Biochemie Zentrum der Biologischen Chemie Universität Frankfurt a M., West Germany); Wacker, A. *Eur. J. Cancer* 11(7):517-519; 1975.

The ability of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) to inhibit rat liver DNA methylase activity was investigated. DNA methylase (from male Wistar rats) was isolated and the enzyme activity was assayed by incubating 3 to 4 mg of enzyme and 0.6 mg *Escherichia coli* B DNA with MNNG. Unbound carcinogen was removed, and the rate of methylation was measured. The specific activity of the enzyme preparation was about 30 pmoles of incorporated methyl groups per mg protein. The product of the enzyme reaction was chromatographically identified as DNA 5-methyl cytosine. Addition of MNNG to the assay system inhibited enzyme activity in a dose-dependent manner. Pretreatment of methyl acceptor DNA did not change its ability to serve as a substrate in the assay system, whereas pretreatment of the enzyme produced complete inactivation of the enzyme. The removal of MNNG from the system did not result in recovery of enzyme activity, indicating that the carcinogen-induced changes were permanent. The sensitivity of free and DNA-bound DNA methylase were compared by adding MNNG to the assay system either before the reaction started or at different times and various doses after initiation of the reaction. Preincubation led to the formation of a stable complex; however, the sensitivity of free and bound DNA was similar. No difference in sensitivity to MNNG by DNA methylating enzymes extracted from different tissues (calf thymus mouse liver, Ehrlich

ascites tumor) was observed. The biological function of 5-methyl-cytosine is unknown. It is suggested that such an alteration of primary structure of chromosomal DNA may modulate the effects of nitrosoguanidines.

- 5483 LABELED METABOLITES OF POLYCYCLIC AROMATIC HYDROCARBONS. III. 3-, 7-, AND 9-HYDROXY-BENZO[*a*]PYRENES-G-³H. (Eng.) Duncan, W. P. (Midwest Res. Inst., 425 Voker Blvd., Kansas City, Mo. 64110); Ogilvie, E. J., II; Engle, J. F. *J. Labeled Compd.* 11(3):461-464; 1975.

Definitive studies of the oxidative metabolism of benzo[*a*]pyrene require the availability of highly pure radiolabeled oxygenated derivatives. A rapid and efficient method has been developed for the tritiation of 3-, 7-, and 9-hydroxybenzo[*a*]pyrenes (3-, 7-, and 9-HOBP), which have been implicated in such studies. The method, a modification of the procedure reported by Garnett for the tritiation of aromatic hydrocarbons and substituted benzenes, is based on the use of ethylaluminum (EADC) catalyst with tritiated water as the isotope source. EADC (30 µl) and carbon disulfide (370 µl) are added to a vial charged with HOBP (13.4 mg, 0.05 mM) and then purged for ten minutes with dry nitrogen. Two minutes after the addition of EADC and carbon disulfide, tritiated water (83 µl), at specific activity of 5 Ci/ml or 26.4 Ci/ml, is added, and the vial is shaken for 2-3 min. One milliliter of cold water is then added, and the precipitated solid is extracted with benzene:ethyl acetate. The procedure yields compounds with a chemical and radiochemical purity of ≥ 98%. Higher specific activity products are obtained when high specific activity water is used, but no significant changes in purity are observed.

- 5484 *N*-NITROSOMORPHOLINE AND *N*-NITROBUTYLAMINE-STIMULATED DNA SYNTHESIS IN BHK-21/C13 CELLS. (Eng.) Kimble, C. E. (Dept. Nutr. Food Sci., Massachusetts Inst. Technol., Cambridge); Gorczyca, P. A.; Reynolds, R. G. *Mutat. Res.* 31(3):153-161; 1975.

The effects of *N*-nitrosobutylamine, *N*-nitrosomorpholine, and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine on non-semiconservative DNA synthesis, and the types of chromosome aberrations elicited by it, were examined in BHK-21/C13 Syrian hamster cells. BHK-21/C13 cells were grown for 24 hr in bromodeoxyuridine (4 µg/ml), treated with the nitrosamines for two hours, and labeling for four hours in [³H]bromodeoxyuridine (3 µCi:1 ml). DNA was isolated and analyzed in isopycnic gradients, and the relative levels of repair replication were determined on the basis of the cpm/µg in the purified DNA. To estimate chromosome aberrations, dividing cells were arrested at metaphase with colchicine. The cultures were pretreated for 15 min in 1% sodium citrate solution, fixed in ethanol:acetic acid, air dried, stained in 2% aceto-orcein, dehydrated, and mounted. The frequency of chromatid aberrations and the incidence of metaphase plates were estimated for the same preparations. The results indicated that repair replication oc-

curred after treatment with N-nitrosobutylamine and N-nitrosomorpholine. The specific activities of the DNA in the cells after rebanding three times in the gradient were (in cpm/ μ g): control, 1.7; N-nitrosobutylamine (50 μ g/ml), 32.7; and N-nitrosomorpholine (100 μ g/ml), 11.0. The aberrations caused by N-nitrosomorpholine included fragments, gaps, breaks, and exchanges of both chromatid and chromosome type. The most frequent aberrations were the dicentric followed by rings, chromosome breaks, and chromatid gaps. N-Methyl-N'-nitro-N-nitrosoguanidine elicited a higher frequency of chromatid breaks than did dicentric. Concentrations of 100 μ g/ml N-methyl-N'-nitro-N-nitrosoguanidine suppressed mitosis completely. Sixty-two percent of the cells treated with 10 μ g/ml N-methyl-N'-nitro-N-nitrosoguanidine were aberrant compared to 43.4% of the cells treated with 1 μ g/ml. With N-nitrosobutylamine, chromatid breaks also occurred at the highest frequency followed by dicentric and chromosome breaks. The given dose of N-nitrosomorpholine was calculated to have induced the insertion of 15.3×10^8 bases/ μ g DNA, and N-nitrosobutylamine was calculated to have induced 50.8×10^8 bases/ μ g DNA. It is suggested that the induction of a higher proportion of dicentric by N-nitrosomorpholine than by the other two compounds may be a manifestation of double polynucleotide chain breaks that are present prior to chromosome replication and are themselves replicated resulting in dicentric at the subsequent metaphase.

- 5485 "K-REGION" OXIDES AND RELATED OXIDIZED METABOLITES OF CARCINOGENIC AROMATIC HYDROCARBONS. (Eng.) Harvey, R. G. (Ben May Lab., Univ. Chicago, Ill.); Goh, S. H.; Cortez, C. *J. Am. Chem. Soc.* 97(12):3468-3479; 1975.

A general synthesis of "K-region" oxides from the parent polycyclic hydrocarbons *via* the corresponding cis dihydrodiols, quinones, and trans dihydrodiols is described. The general synthetic scheme involves the following sequence: (1) generation of the "K-region" cis dihydrodiols *via* interaction of the corresponding hydrocarbons with osmium tetroxide, (2) oxidation with dimethyl sulfoxide and sulfur trioxide-pyridine complex to the quinones, (3) reduction with lithium aluminum hydride to yield the related trans dihydrodiols, and (4) cyclization of the latter with the dimethyl acetal of dimethylformamide to the desired K-oxides. All the intermediates, the cis and trans diols, as well as the quinones, are themselves K-region oxidized intermediates of interest as potentially biologically active metabolites. By adaptation of the general procedure, the related K-phenols (both isomers) and the previously unknown K-hydroquinones were also obtained. The K-oxidized metabolites of benzo[a]pyrene, 7,12-dimethylbenz[a]anthracene, and dibenz[a,h]anthracene in addition to those derived from pyrene, phenanthrene, benz[a]anthracene, and chrysene were prepared by this procedure. Several alternative synthesis of the K-oxides were also carried out, including an osmium tetroxide-catalyzed periodate oxidation of 7,12-dimethylbenz[a]anthracene to the corresponding K-region dialdehyde followed by cyclization. The mechanism and stereochemistry of reduction of the quinones with

lithium aluminum hydride were also investigated. Acid-catalyzed reaction of the diol diacetates gave two isomeric phenol acetates providing convenient synthetic access to the K-phenols. However, 5-acetoxy-7,12-dimethylbenz[a]anthracene was apparently formed regio-specifically, and 5-hydroxy-7,12-dimethylbenz[a]anthracene existed preferentially in the keto structure. The K-phenols of benzo[a]pyrene and dibenz[a,h]anthracene did not exhibit this property. A correlation between preferential existence of K-phenols in the keto form and carcinogenic activity apparently does not exist.

- 5486 VITAMIN A AND BENZO(a)PYRENE CARCINOGENESIS IN THE RESPIRATORY TRACT OF HAMSTERS FED A SEMISYNTHETIC DIET. (Eng.) Smith, D. M. (Dept. Nutr. Food Sci., Massachusetts Inst. Technol., Cambridge); Rogers, A. E.; Newberne, P. M. *Cancer Res.* 35(6):1485-1488; 1975.

The effect of adequate or increased intake of vitamin A on benzo(a)pyrene induction of respiratory tract tumors was investigated in hamsters fed a semisynthetic diet. Male Syrian golden hamsters were obtained from dams fed a diet containing 10 μ g/g retinoic acid during lactation. The males were fed the semisynthetic diet and given 12 weekly intratracheal instillations of benzo(a)pyrene (3 mg) adherent to 3 mg Fe_2O_3 . Either 100, 1,600, or 2,400 μ g retinyl acetate (RA) was then administered intragastrically each week in two divided doses. Half of the animals in each group were housed conventionally; the other half were housed in laminar flow units. Hepatic and serum vitamin A levels were markedly increased in hamsters given 1,600 or 2,400 μ g RA/wk. Controls given 100 μ g had levels of 17 μ g/g and 150 μ g/100 ml. In hamsters housed conventionally, increased RA intake was associated with an increased incidence of benign respiratory tract tumors. In all groups of hamsters housed in laminar flow units there was a longer period to death with respiratory tract tumor than in conventionally housed hamsters; RA intakes of 1,600 or 2,400 μ g/wk were associated with a lower incidence of respiratory tract tumors (59 and 57%, *vs.* 71% of those getting 100 μ g RA/wk). Laminar flow housing significantly reduced the incidence of respiratory tract infection in nontumor-bearing hamsters. Squamous papillomas of the forestomach were found in about 25% of all hamsters given either of the two higher levels of RA, compared to 50% of hamsters given 100 μ g RA/wk ($p < 0.005$). Statistically significant suppression by retinyl acetate of the benzo(a)pyrene-induced respiratory tract tumors was not found in this study.

- 5487 NO DIFFERENCES IN BENZO(a)PYRENE HYDROXYLASE ACTIVITY IN THE HUMAN IMMATURE PLACENTA AND IN THE HUMAN FETAL LIVER FROM CIGARETTE SMOKING AND NONSMOKING WOMEN. (Eng.) Schlegel, E. (Pharmakologisches Institut der Freien Universitt Berlin, Thielallee 69/73, D-1000 Berlin 33/Germany); Scholz, H. *J. Perinat. Med.* 2(3):189-195; 1975.

Benzo(a)pyrene hydroxylase (BP hydroxylase) activity was assayed in the immature placentas of smoking and

nonsmoking women undergoing therapeutic abortion in the 11th and 19th wk of pregnancy; enzyme activity in their unborn fetuses was also assayed. In the nonsmoking group the activity of this enzyme was not detectable in four placentas. In the other five placentas the hydroxylation rate of BP ranged from 0.088-1.510 μg 3-hydroxy-BP/g tissue/hr. In the placentas obtained from the smokers, three had no BP hydroxylase activity. These women smoked 3-20 cigarettes daily. The other six women smoked almost the same daily number of cigarettes, and the rate of BP hydroxylation ranged from 0.068-1.176 μg 3-hydroxy-BP/g tissue/hr. The mean \pm S.D. of BP hydroxylase activity was 0.252 ± 0.489 and 0.345 ± 0.413 μg 3-hydroxy-BP/g tissue/hr in the nonsmoking and cigarette smoking group, respectively. These data suggest that between the 11th and 19th wk of pregnancy, cigarette smoke has little or no stimulatory effect on placental BP hydroxylase activity. Furthermore, factors other than components of cigarette smoke might enhance enzymatic BP hydroxylation: the highest enzyme activity (1.510 μg 3-hydroxy-BP/g tissue/hr was found in the placenta of a nonsmoker who was taking high doses of barbituates and other drugs. In the fetal liver the activity of enzymes that hydroxylate BP and N-demethylate ethylmorphine was demonstrated. No correlation was observed between the levels of BP hydroxylase activity in the fetal liver and in the placenta. In fetal tissues the capacity to metabolize drugs and foreign compounds does not necessarily imply a detoxification mechanism, since metabolites derived from these reactions might be harmful for the rapidly proliferating and differentiating fetal tissues.

- 5488 PRODUCTION OF EPITHELIAL AND MESENCHYMAL TUMOURS WITH RAT LIVER CELLS TRANSFORMED *IN VITRO*. (Eng.) Montesano, R. (International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69008 Lyons, France); Saint Vincent, L.; Drevon, C.; Tomatis, L. *Int. J. Cancer* 16(4):550-558; 1975.

Studies on dimethylnitrosamine (DMN)- and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced adenocarcinomas and fibrosarcomas in the epithelial-like cells of rat liver are described. Epithelial-like cells originating from the livers of 10-day and 8-wk-old BD rats were established in culture. The cells were treated *in vitro* twice for 1 or 4 wk with 100 $\mu\text{g}/\text{ml}$ DMN or 10 $\mu\text{g}/\text{ml}$ MNNG. Although some structural changes were observed in treated cells, it was not possible to score for morphological transformation *in vitro*. Newborn syngeneic rats were injected sc or ip with 1.5×10^6 to 2×10^6 treated or 1.5×10^6 to 5×10^6 control cells at various times up to 38 wk from the beginning of treatment with the carcinogen. Following the injection of DMN-treated cells, a total of 32 of the 42 injected rats developed tumors, of which 17 were epithelial, ten were carcinosarcomas and five were fibrosarcomas. Following the injection of the MNNG-treated cells into 61 rats, a total of 30 tumors were observed, including eight carcinomas, nine carcinosarcomas and 13 fibrosarcomas. Tumors, mainly of the mesenchymal type, were also observed in rats

inoculated with control cells, but at a lower frequency. The observation of mesenchymal tumors is attributed to the presence of a mixed population of epithelial and mesenchymal cells in the original culture.

- 5489 THE CARCINOGENIC EFFECT OF DIMETHYLNITROSAMINE ON THE CHINESE HAMSTER (*CRICETULUS GRISEUS*). (Eng.) Reznik, G. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule, Hannover, 3000 Hannover-Kleefeld, Karl-Wiechert-Allee 9, West Germany). *Cancer Lett.* 1(1):25-28; 1975.

Studies were undertaken to compare the reaction of Chinese hamsters to dimethylnitrosamine (DMN) treatment with the reactions previously reported for other hamster species. Three groups of Chinese hamsters (20 males, 20 females per group) received weekly sc injections for life of DMN at doses of 0.20, 0.10, and 0.05 of the LD_{50} . Of these animals, 82-100% developed tumors of vascular origin. The neoplasms were primarily hepatic hemangioendotheliomas, and their incidence was unrelated to dose or sex; this is in contrast to the incidences reported previously for European hamsters. Although animals in the low dose group received a total dose one-third that of the highest dose group, their survival times were only slightly longer. In comparing the incidence rates of DMN-induced tumors in European, Syrian, and Chinese hamsters, the Chinese hamsters had the most liver neoplasms in all dosage groups.

- 5490 ORAL CONTRACEPTIVES AS RELATED TO CANCER AND BENIGN LESIONS OF THE BREAST. (Eng.) Fasal, E. (California State Dept. Health, Berkeley, Calif. 94704); Paffenbarger, R. S., Jr. *J. Natl. Cancer Inst.* 55(4):767-773; 1975.

A case-control study was conducted to search for any relationship between use of oral contraceptives and development of breast cancer or benign breast disease. Women less than 50 yr old with diseases were matched with two controls by age, race, religion, and hospital. Home interviews elicited information on oral contraceptive use and other host and environmental factors. The study population comprised 1,770 women, including 452 with breast cancer and 446 with benign breast disease. The relative risk of developing cancer or benign disease was measured by matched set and summary chi-square analyses. Although the relative risk of developing breast cancer among those women who had ever used oral contraceptives was 1.1, the risk among women using oral contraceptives for 2-4 yr was 1.9 (significantly increased). This risk estimate reached 2.5 for the 2-4 yr users if they were still taking oral contraceptives when entered into study. Moreover, prior biopsy for benign breast disease increased the cancer risk among long-term users by as much as 11-fold. The relative risk of breast cancer did not vary by age, interval since first use, earliest year of use, or interval since last use. These results could be interpreted to indicate that oral contraceptives did not induce

breast cancer but may have accelerated the growth rate of preexisting breast cancer. The relative risk of developing benign breast disease among ever-users of oral contraceptives was 0.8 (significantly reduced); it decreased with longer duration of use until it reached 0.2 for women who took these hormones eight yr or more. The relative risk of benign breast disease, was not affected by earliest year of use or interval since last use. It is concluded that oral contraceptives reduced the incidence of benign breast disease, but that use of steroid hormones is ill-advised for women with already established benign breast disease.

5491 CHROMOSOMES AND ORAL CONTRACEPTIVES:
ABERRATIONS IN RELATION TO NEOPLASIA.

(Eng.) Mills, J. (Res. Dep., Marie Curie Mem. Found., Oxted, England); Bishun, N.; Williams, D.; Raven, R. W. *Clin. Oncol.* 1(2):141-147; 1975.

Chromosome abnormalities were investigated in peripheral blood WBC cultures of 185 women who had taken oral contraceptives. Their progeny (153 babies) and 181 control women who had used no form of contraception were also studied. No significant difference in the frequencies of aberrations were found between the test and control mothers. Minor differences were found in the test babies and a group of 157 control babies of the control women. It was assumed that the incidence of aberrations would be exaggerated where the mothers, in addition to taking the oral contraceptives, had been exposed to external environmental hazards (i.e., x-irradiation during pregnancy or occupational exposure to carcinogenic compounds). No such increase was observed and the possible relationship of the combined effects of the contraceptives and external hazards are discussed.

5492 STUDIES ON THE METABOLISM OF DIMETHYLNITROSAMINE IN THE RAT. I. EFFECT OF DOSE, ROUTE OF ADMINISTRATION AND SEX. (Eng.) Phillips, J. C. (British Ind. Biol. Res. Assoc., Carshalton, England); Lake, B. G.; Heading, C. E.; Gangolli, S. D.; Lloyd, A. G. *Food Cosmet. Toxicol.* 13(2):203-209; 1975.

Dimethylnitrosamine (DMN) metabolism was studied in male and female Wistar rats with particular attention to the po route of administration. [^{14}C]DMN in 0.9% NaCl (0.2 ml/100 g) was administered ip, sc, iv, and by po intubation. ^{14}C exhaled by the rats was trapped in ethanolamine-2-ethoxyethanol. [^{14}C]DMN solution was also injected into the stomach and into a loop of small intestine between 10 and 30 cm from the pylorus; following absorptive periods of 6-30 min for stomach and 0-30 min for intestine, the tissues were assayed for radioactivity and DMN concentration was determined by gas-liquid chromatography. Considerable inter-animal variation in the rate of DMN metabolism was observed. However, the rate of metabolism appeared to be related to the dose over the entire range studied (0.1-50 mg/kg). Immature animals metabolized DMN at a significantly higher rate than mature animals of the same sex. The rate of

metabolism was similar for all three parenteral routes of injection; this suggested the likelihood of a common mechanism for the disposition and metabolism of DMN in the body. The initial rate of $^{14}\text{CO}_2$ excretion was slower following po administration than the rates of the parenteral routes. The $^{14}\text{CO}_2$ produced over the seven-hour experimental period was, however, similar for all routes of administration, as was the ^{14}C present in urine during the 24 hr following dosing. Studies of the disappearance of [^{14}C]DMN from the stomach and small intestine indicated that the lower rate of metabolism after po administration was probably due to slower absorption of DMN from the stomach. The kinetics of the disappearance of radioactivity from the small intestine were shown to vary with the intraluminal concentration of [^{14}C]DMN, following a monoexponential curve at very low concentration (0.001 mg/ml) and a biexponential curve at higher concentrations (up to 5 mg/ml). The results suggest that a significant proportion of DMN administered at low levels is metabolized during absorption; this factor cannot be ignored when considering the levels of DMN in food.

5493 EFFECTS OF EXPOSURE OF NEONATAL MICE TO 17β -ESTRADIOL ON SUBSEQUENT AGE-INCIDENCE AND MORPHOLOGY OF CARCINOGEN-INDUCED MAMMARY DYSPLASIA. (Eng.) Warner, M. R. (Baylor Coll. Medicine, Houston, Tex. 77025); Warner, R. L. *J. Natl. Cancer Inst.* 55(2):289-298; 1975.

The effects of exposing neonates to estrogen in terms of subsequent age-incidence of carcinogen-induced mammary dysplasia was studied in BALB/c mice. The mice were given 40 μg 17β -estradiol in 0.02 ml aqueous microsuspension sc on each of the first five days of life. Two doses of 0.5 mg 7,12-dimethylbenz(a)anthracene in 0.2 ml cottonseed oil were given po at several ages: (a) before puberty, (b) during active mammary growth, and (c) at six months of age (the time when spontaneous dysplasias begin to appear in normal animals). Mice were killed either at 20 wk of age or, in the older group, at ten months of age. Termination was scheduled at ten weeks after the second carcinogen feeding. Dysplasias were classified grossly according to morphology with the dissection microscope. The average number of dysplasias per dysplasia-bearing animal tended to be higher in estrogen-treated than in untreated mice. The relative percentages of various morphologic types of dysplasias differed in hosts that received different treatments. Ectopic pituitary implantation in 4-wk-old mice and carcinogen administration at 8 and 10 wk to otherwise untreated mice resulted in an average of 118 dysplasias per animal, significantly more lesions than in any other group. An average of 6.9 dysplasias per mouse was seen in the group given a pituitary implant but no carcinogen or estrogen. Another group receiving carcinogen only, had an average of 4.8 dysplasias per animal. The group of mice that received estrogen as neonates, a pituitary implant at four weeks of age, and carcinogen at 8 and 10 wk, had an average of 23.9 dysplasias per animal. Characteristic regions of cystic response were noted, either in substantial areas of some mammary glands or in the entire mammary systems of

some mice. This cystic response occurred most often in glands of estrogen-treated mice that had received carcinogen early in life. Feeding of 7,12-dimethylbenz(a)anthracene at any age or injection of estrogen in neonates appeared to be a requisite for the cystic response. This suggests that 7,12-dimethylbenz(a)anthracene and neonatal treatment with estrogen could have similar mechanisms of action and that they may synergize to produce a more intense effect. These findings emphasize the potential hazards of exposure of human neonates to estrogens, which may come from maternal contraceptives or other hormone therapy or from maternal dietary sources.

5494 STEROL METABOLISM XXXIV: ON THE DERIVATION OF CARCINOGENIC STEROLS FROM CHOLESTEROL. (Eng.) Smith, L. L. (Univ. Texas Medical Branch, Galveston, Texas 77550); Kulig, M. J. *Cancer Biochem. Biophys.* 1(2):79-84; 1975.

Cholesterol was incubated in cold chloroform solution with cholesterol 7 α - or 7 β -hydroperoxides, with 17 β -hydroxy-5 α -cholest-6-ene-5-hydroperoxide, or with cumene hydroperoxide. These reactions gave low yields of 5,6 α -epoxy-5 α -cholestan-3 β -ol, a recognized carcinogen, and 5,6 β -epoxy-5 β -cholestan-3 β -ol. Product proportions of 1:8 to 1:11 were estimated chromatographically following lithium aluminum hydride reduction of the sterol epoxide mixtures. These results suggest means by which the sterol carcinogen might be formed in tissues.

5495 STUDIES ON 17 β -HYDROXYSTEROID DEHYDROGENASE IN HUMAN ENDOMETRIUM AND ENDOMETRIAL CARCINOMA. III. PARTIAL PURIFICATION AND CHARACTERIZATION OF THE MICROSOMAL ENZYME. (Eng.) Pollow, H. (Sterilität und Familienplanung im Klinikum Steglitz, Freie Universität Berlin, Germany); Schubert, H.; Pollow, B. *Acta Endocrinol. (Kbh.)* 2(2):355-364; 1975.

The partial purification, reaction kinetics, and substrate specificity of microsomal 17 β -hydroxysteroid dehydrogenase (17 β -HSD) were investigated. Microsomal 17 β -HSD obtained from human secretory endometrium or endometrial carcinoma was solubilized (70%) with triton X-100 and purified four-fold by ammonium sulfate precipitation and isoelectric focusing. The partially purified 17 β -HSD was found stable at 4 C in the presence of glycerol for at least 48 hr. The 17 β -HSD activity of crude microsomes from secretory endometrium increased almost linearly with protein concentration and incubation time. The temperature optimum was 42 C; the optimal pH was 9.4 for the oxidative reduction of estradiol-17 β to estrone, while a pH of 6.5 was optimum for the reductive reaction. NAD was the preferred cofactor. The K_m values for proliferative endometrium, secretory endometrium, and undifferentiated endometrial carcinoma were 5.0×10^{-6} M, 1×10^{-6} M, and 3.5×10^{-6} M, respectively; velocity was highest in the secretory endometrium. Sulphydryl group blocking agents exerted a strong inhibitory effect, as did the metal ions Mg^{2+} , Zn^{2+} , and Cu^{2+} .

While testosterone and androstenedione were also capable of serving as substrates, they were interconverted more slowly than estradiol and estrone. As the kinetic parameters were found very similar to those of the cytoplasmic 17 β -HSD previously described, it was indicated that 17 β -HSD is "secreted" by the microsomes. It is suggested that the differences in enzyme activity in normal and neoplastic endometrium are due to changes in enzyme concentration or some more complicated mechanism.

5496 FECAL STEROIDS IN POLYPOSIS COLI AND ILEORECTOSTOMY PATIENTS. (Eng.) Watne, A. L. (Charleston Foundation, West Virginia Univ., Morgantown, W. Va. 26506); Core, S. K. *J. Surg. Res.* 19(3):157-161; 1975.

Neutral and acid steroids in fecal samples from patients with familial polyposis were studied before (seven patients) and after (five patients) ileorectostomy. Cholesterol, cholic acid, and chenodeoxycholic acid were significantly higher in the familial polyposis group prior to surgery than in seven normal controls. In the polyposis group, ileorectostomy resulted in complete disappearance of the bacterial metabolite coprostanol. Three years postoperative, the polyposis patients were unable to hydrogenate cholesterol. Chenodeoxycholic and cholic acids were also significantly higher in the ileorectostomy patients. Lithocholic and deoxycholic acids were not significantly different in the polyposis coli group but were significantly lower in the ileorectostomy group. The differences in the fecal steroid patterns in control subjects, polyposis coli subjects, and ileorectostomy subjects may be caused by different fecal flora.

5497 TESTING OF SOME BENZIDINE ANALOGUES FOR MICROSOMAL ACTIVATION TO BACTERIAL MUTAGENS. (Eng.) Garner, R. C. (Dept. Experimental Pathology and Cancer Res., Univ. Leeds, 171 Woodhouse Lane, Leeds, LS2 3AR, Yorkshire, U.K.); Walpole, A. L.; Rose, F. L. *Cancer Lett.* 1(1):39-42; 1975.

Analogues of benzidine were assayed for mutagenic activity towards *Salmonella typhimurium* TA 1538 in the presence and absence of a liver enzyme preparation. Purified 3,3'-dichlorobenzidine had some direct mutagenic activity; this was increased over 50-fold by addition of mixed-function oxidase preparation from the liver of a phenobarbitone-pretreated rat. In the presence of the liver preparation, 3,3'-dichlorobenzidine gave 7,520 His⁺ revertants/plate, compared to 640 for benzidine. Both compounds were at 100 μ g/plate. 3,3',5,5'-Tetrafluorobenzidine (100 μ g/plate) gave 1040 revertants/plate. 3,3',5,5'-Tetramethylbenzidine gave only 15 revertants/plate even when the liver was added. 3,3',-Dianisidine had slight mutagenic activity in the presence of liver (82 revertants/plate). Dichlorobenzidine is used in dye manufacture in the United Kingdom. The results indicate that exposed workers should be followed for development of cancer.

- 5498 THE HISTOLOGICAL CHANGES IN THE LIVER AND IN THE URINARY BLADDER IN MICE FED BENZIDINE WHOSE BLADDERS CONTAINED GLASS BEADS. (Eng.) Miyakawa, M. (Kyoto City Hosp., Nakagyo-ku, Kyoto 604, Japan); Yoshida, O. *Hinyokika Kyo* 21(1):63-66; 1975.

The induction of bladder tumors in mice each with one glass bead in their bladder was attempted using 0.2% benzidine freely administered in the diet. Female mice of the *d,d*-strain were divided into three groups of 50 mice each: group 1 ate a normal diet and bore glass beads; group 2 was fed 0.2% benzidine and bore glass beads; and group 3 was fed 0.2% benzidine and bore no glass beads. Forty-five mice of groups 1 and 2 and 15 mice from group 3 survived at least 140 days. There were no bladder tumors in any of the surviving mice. Hyperplasia of the bladder epithelium was common in both glass bead-bearing groups; group 1 had an 87.5% incidence and group 2 had a 96.6% incidence. Group 3 showed only a 40% incidence of bladder hyperplasia. Liver changes were seen in groups 2 and 3; the incidence of hepatoma was 34.4% and 44.4% among group 2 and 3, respectively. Of groups 2 and 3 combined, other hepatic changes were: hyperplastic nodules with atypical area, 14%; diffuse atypical area, 22%; hyperplastic nodules alone, 20%; and other changes, 6%. The hepatomas varied histologically in structure. The authors conclude that benzidine seems to be hepatocarcinogenic to female *d,d* strain mice but not carcinogenic to the bladder.

- 5499 THE SPECIFICITY OF DIFFERENT CLASSES OF ETHYLATING AGENTS TOWARD VARIOUS SITES IN RNA. (Eng.) Singer, B. (Dep. Mol. Biol. Virus Lab., Univ. California, Berkeley); Fraenkel-Conrat, H. *Biochemistry* 14(4):722-782; 1975.

The alkyl products of neutral *in vitro* ethylation of TMV-RNA and unfractionated HeLa cell RNA by [¹⁴C]diethyl sulfate, [¹⁴C]ethyl methanesulfonate, and [¹⁴C]ethyl nitrosourea were determined and compared with the methyl products obtained when TMV-RNA is similarly treated with dimethyl sulfate and methyl methanesulfonate. TMV-RNA (1 mg) in 0.7 ml 0.75 M, pH 7.3 cacodylate buffer was reacted with 20-60 l diethyl sulfate, 20 l ethyl methanesulfonate, or 15 mg ethyl nitrosourea, for 15 min to three hr. TMV-RNA (0.5 mg), in 35 ml 0.75 M, pH 7.3 cacodylate buffer was reacted with 20 l dimethyl sulfate, or 10 l methyl methanesulfonate for three hr. HeLa cell RNA (0.5 mg) was ethylated under the same conditions as those used for ethylation of TMV-RNA, except that half the quantity of reagent was used. Three chromatographic systems and electrophoresis were used to separate the various alkyl derivatives after acid hydrolysis or enzyme digestion. Identified ethyl bases accounted for more than 85% of the total radioactivity of [¹⁴C]ethyl methanesulfonate- and [¹⁴C]diethyl sulfate-treated TMV-RNA. Phosphate alkylation accounted for about 13 and 1%, resp. [¹⁴C]Ethyl nitrosourea-treated TMV-RNA caused considerably more phosphate alkylation. It appears that ethyl nitrosourea preferentially alkylates oxygen, and that formation of phosphotriesters is the predominant chemical event. Since

the number of ethyl groups introduced into TMV-RNA by ethyl nitrosourea was similar to the number of lethal events, it is concluded that phosphate alkylation leads to loss of infectivity. None of the three ethylating agents studied was strongly mutagenic on TMV-RNA or TMV. Unfractionated HeLa cell RNA was ethylated primarily in an acid labile manner, which is attributed to its high content of low molecular weight RNA, rich in terminal phosphates which alkylate readily. The role of phosphate alkylation in *in vivo* mutagenesis remains to be established but it is suggested that the extent of this reaction may correlate better with the oncogenic effectiveness of different ethylating agents, than with the extent of any base reaction.

- 5500 INDUCTION OF OVARIAN TUMOR IN RATS WITH N-BUTYLNITROSOUREA. (Eng.) Fukunishi, R. (Ehime Univ. Sch. Medicine, Matsuyama 790-91, Japan); Wang, H.-H.; Yoshida, A.; Yoshida, H.; Hirota, N.; Mori, H. *Gann* 66(3):323-325; 1975.

Pathological studies were performed on ovarian tumors induced by N-butyl nitrosourea. Adult Sprague-Dawley rats were treated with po or im administration of 300 mg/kg N-butyl nitrosourea 1-3 times at biweekly intervals. Tumors were induced in 8.2% of the rats. Tumors were also induced in 10.7% of the rats injected im with a single dose of 300 mg/kg of the drug. Histologically the tumor was a clear-cell adenoma similar to embryonal testicular tissue. The morphological features (sparse, small mitochondria, numerous ribosomes, poorly developed endoplasmic reticulum, some dense bodies, and vacuoles containing floccular material) were observed by electron microscopy. The authors state: "These morphological features suggest that the tumor cells retain secretory function and might have originated from an epithelial element of the embryonal mesodermal tissue, but it was not possible to find their histogenesis in the normal mature ovarian components."

- 5501 EFFECT OF POLYCHLORINATED BIPHENYLS (AROCOR 1254) ON INDUCIBLE AND REPRESSIBLE MICROSOMAL N-DEMETHYLASES IN THE MOUSE AND RAT. (Eng.) Argus, M. F. (U.S.P.H.S. Hosp., 210 State St., New Orleans, La. 70188); Bryant, G. M.; Pastor, K. M.; Arcos, J. C. *Cancer Res.* 35(6):1574-1579; 1975.

A comparative study of the effects of Aroclor 1254 (40 and 500 mg/kg, ip), 3-methylcholanthrene (80 or 160 mg/kg, ip), and starvation on hepatic dimethylnitrosamine (DMN) demethylase (a repressible enzyme) and azo dye N-demethylase (an inducible enzyme) was carried out in male Swiss-Webster mice and male Sprague-Dawley rats. As previously observed with polycyclic hydrocarbons and phenobarbital, Aroclor administration in rats resulted in a significant increase in liver tissue proliferation and azo dye N-demethylase activity but in a very substantial decrease in DMN demethylase activity. While the induction of liver tissue proliferation and azo dye N-demethylase activity was maintained in mice, Aroclor had no effect on DMN demethylase.

Starvation, which is known to substantially increase DMN demethylase levels in rats, brought about a small but significant induction of DMN demethylase in mice. The repression of DMN demethylase in Aroclor-treated rats provides further evidence for the multiplicity of cytochrome P-450-dependent mixed-function oxidases.

- 5502 SPECIFIC CARCINOGENIC EFFECT OF *N*-METHYL-*N*-NITROSOUREA ON THE MIDVENTRAL SEBACEOUS GLAND OF THE GERBIL (*MERIONES UNGUICULATUS*). (Eng.) Laas, H. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, 3000 Hannover-Neerfeld, Karl-Weichert-Allee 9, West Germany); Wilfrich, J.; Kmoch, N.; Mohr, U. *J. Natl. Cancer Inst.* 55(3):637-640; 1975.

To test the possibility that *N*-nitroso compounds may have different organotropic effects in different laboratory animals, the effect of repeated injections of *N*-methyl-*N*-nitrosourea (NMU) was tested in gerbils (*Meriones unguiculatus*). Seventy-two 9- to 12-wk-old male and female gerbils were given NMU once weekly for 15 wk at doses related to the mean lethal dose (LD50): 5(1/5 LD50) or 2.5(1/10 LD50) mg/kg. Sixteen animals (nine males, seven females) that were treated with the high dose and 11 animals (seven males, four females) treated with the low dose developed tumors, primarily of the species-specific midventral sebaceous gland. These neoplasms were histologically classified as sebaceous adenomas or carcinomas of varying differentiation. These effects contrast with the reported effects of NMU on rats.

- 5503 ETHIONINE-INDUCED CHANGES IN RAT LIVER TRANSFER RNA METHYLATION. (Eng.) Wainfan, H. (Lindsley F. Kimball Res. Inst. of New York Blood Center, New York, N.Y. 10021); Moller, M. L.; Schio, F. A.; Balis, M. E. *Cancer Res.* 35(10):2830-2835; 1975.

Ethionine-induced changes in rat liver transfer RNA (tRNA) methylation were investigated. Female CFN star rats were given sodium pentobarbital (50 mg/100 ml) in their water three days prior to drug treatment. Control animals also received pentobarbital. Experimental animals were given ip injections for either 3 or 5 consecutive days with a daily dose of DL-ethionine (250 mg/kg) and adenine (20 mg/kg) suspended in carboxymethylcellulose and were sacrificed by decapitation on the following morning. Enzyme extracts were derived from the excised liver. The tRNA was prepared from *Escherichia coli* and from the liver of experimental rats and controls injected with adenine alone. The RNA dissolved in 1.6 ml of 2 M NH₄OH was assayed for radioactivity in a scintillation counter. Each of these tRNAs was tested for its ability to act as a methyl group acceptor in the *in vitro* reaction catalyzed by the tRNA-methylating enzymes extracted from livers of control rats. The findings were that incompletely methylated tRNA was present in the livers of rats treated with large doses of ethionine for a short time and implied that tRNA methyla-

tion was inhibited *in vivo* after ethionine administration. A possible sequence of events following administration of ethionine would be: (1) production of inhibitors, (2) reduction in methylation of tRNA, (3) derepression of the locus for tRNA methylase synthesis, and (4) nearly normal methylation due to excess enzyme. The *in vivo* results are extrapolated from the *in vitro* observations.

- 5504 ABSENCE OF NITROSO FORMATION FROM [¹⁴C]-METHOMYL AND SODIUM NITRITE UNDER SIMULATED STOMACH CONDITIONS. (Eng.) Han, J. C-Y. (Biochemicals Dept., Experimental Station, E.I. du Pont de Nemours & Co., Inc., Wilmington, Del., 19898). *J. Agric. Food Chem.* 23(5):892-896; 1975.

The formation of nitrosomethomyl from methomyl (*S*-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate) and residual sodium nitrite in cured meat macerates under simulated stomach conditions was investigated. Methomyl is the active ingredient in a pesticide registered for use on important food crops. Radio-labeled methomyl (1 ppm) was added to macerates of commercially purchased ham and hot dog containing 16-20 ppm of residual sodium nitrite. These samples were then incubated under simulated stomach conditions (pH 2) for 1 or 3 hr and analyzed for nitrosomethomyl formation by thin layer chromatography. No nitrosomethomyl (< 1 ppb) was found in either meat macerate. The amount of methomyl added (1 ppm, based on solid content) represents a high level of consumed residue, since the highest tolerances for methomyl are in the 1-5 ppm range. There would also be an immediate dilution of pesticide residue in the stomach with other foods containing no methomyl at all. There is thus very little likelihood that nitrites in the diet can combine with methomyl to form detectable amounts of a nitroso compound in the stomach.

- 5505 THE EFFECT OF METHYLATED OXYPURINES ON THE SIZE OF NEWLY-SYNTHESIZED DNA AND ON THE PRODUCTION OF CHROMOSOME ABERRATIONS AFTER UV IRRADIATION IN CHINESE HAMSTER CELLS. (Eng.) Nilsson, K. (Dept. of Genetics and Plant Breeding, Royal Agricultural Coll. of Sweden, S-750 07 Uppsala 7, Sweden); Lehmann, A. R. *Mutat. Res.* 30(2):255-265; 1975.

The inhibitory effects of different methylated oxypurines on postreplication repair of UV-irradiated DNA and their effectiveness in potentiating the UV-induced frequencies of chromosomal aberrations were compared in Chinese hamster cell cultures. Eight methylated oxypurines were tested: caffeine, chlorocaffeine, 8-methoxycaffeine, 8-ethoxycaffeine, 1,7-dimethylxanthine (paraxanthine), 1,3,7,9-tetramethyluric acid. The cells were seeded at 4 x 10⁵ cells/5-cm dish, incubated overnight, UV-irradiated, and then incubated in medium with or without the methylated oxypurine (0.75 mM) immediately after irradiation. After 30 min, the cells were labeled with [³H]thymidine (3.3 µCi/ml) and incubated for another four hours. The size of the DNA in the UV-irradiated, methylated oxypurine-treated cells was calculated from alkaline sucrose sedimentation pro-

files. In another series of experiments, cells were seeded 28-29 hr before irradiation at a density of 4×10^4 cells/ml. Immediately after UV irradiation, the cells were incubated in medium with or without methylated oxypurines and harvested after 14, 18, or 22 hr. Most of the abnormal cells contained multiple aberrations, the majority of which were chromatid breaks and a few exchanges. In the tests of post-replication repair, caffeine and chlorocaffeine were always the most potent inhibitors; tetramethyluric acid was inactive; and the other five derivatives had intermediate effects. Measurements of the potentiation of UV-induced chromosome aberrations showed that treatment with caffeine or chlorocaffeine again had the greatest effect; tetramethyluric acid and theophylline had no potentiating activity, and methoxycaffeine was intermediate. This correlation between effects at the molecular and cytological levels is consistent with the hypothesis that the inhibition of postreplication repair by methylated oxypurines gives rise to the increased production of chromosome aberrations.

5506 BIOTRANSFORMATION OF 1-(4-CHLOROPHENYL)-3,3-DIMETHYLTRIAZENE INTO 3-CHLORO-4-HYDROXYANILINE: INTRAMOLECULAR HYDROXYLATION-INDUCED CHLORINE MIGRATION DURING A CATABOLIC DEGRADATION OF A CHEMICAL CARCINOGEN. (Eng.) Kolar, G. F. (Inst. for Toxicology and Chemotherapy, German Cancer Res. Centre, Heidelberg, West Germany); Schlesiger, J. *Cancer Lett.* 1(1):43-47; 1975.

Urinary excretion products were investigated in ethyl acetate extract from hydrolyzed urine of male Sprague-Dawley rats injected with 1-(4-chlorophenyl)-3,3-dimethyltriazene (65 mg, sc). Five modified anilines were identified by cochromatography with authentic samples combined with specific reactions of their functional groups. 4-Chloro-2-hydroxyaniline (15.1%) and 4-chloroaniline (5.2%) were the most abundant metabolites arising by *in vivo* fission of the diazoamino group. The structures and distribution of 4-hydroxyaniline (< 0.1%), 4-chloro-3-hydroxyaniline (0.7%), and of 3-chloro-4-hydroxyaniline (8.2%) suggested that these metabolites are derived from a common 3,4-epoxy intermediate and arise either by elimination of chlorine, by opening of the epoxide ring, or by an intramolecular hydroxylation-induced chlorine migration, respectively.

5507 THE UV FADING OF HYDROCARBON FLUORESCENCE AND ITS PREVENTION FOR OBSERVATIONS IN SINGLE LIVING CELLS. (Eng.) Kohen, E. (Papanicolaou Cancer Res. Inst., 1155 N.W. 14th St. P.O. Box 23-6188, Miami, Fla. 33123); Salmon, J. M.; Viallet, P.; Kohen, C.; Deumie, M. *Histochemistry* 44(4):357-361; 1975.

The fading of hydrocarbon fluorescence due to the excitation conditions of a modified microspectrofluorometer, as it affects the *in situ* study of carcinogen metabolism, was investigated. Use of a modified design, smaller regions, higher spectral resolution, and increased excitation inten-

sity were found to result in the disappearance of the emission due to intracellularly accumulated polycyclic aromatic hydrocarbons within 10-12 min. A kinetic study of benzo(a)pyrene disappearance noted such disappearance of hydrocarbon fluorescence under excitation at 366 nm as an exponential function of time. However, returning to the excitation condition used in the prototype microspectrofluorometer allowed up to 10-12 min. observations subsequent to microinjection of glucose-6-P, without significant fading. After microinjection of glucose 6-P to EL2 cells having accumulated a polycyclic aromatic hydrocarbon or a heterocyclic hydrocarbon, a sequence of changes was observed in the difference spectrum. The possible relative contribution of NAD(P)H and hydrocarbon metabolites to such sequential changes was uncertain. However, the main obstacle, i.e. the UV fading of hydrocarbon fluorescence, was reasonably prevented by adherence to the prototype excitation conditions.

5508 TESTING THE MUTAGENIC POTENCY OF CHEMICAL SUBSTANCES IN A LINEAR HOST-MEDIATED ASSAY: I. EXPERIMENTAL MICROBIOLOGICAL BASIS. (Eng.) Grafe, A. (Medizinische Forschung, Boehringer Mannheim GmbH, Mannheim, West Germany); Lorenz, R.; Vollmar, J. *Mutat. Res.* 31(4):205-216; 1975.

The experimental conditions and the statistical basis of a host-mediated assay necessary to determine the mutagenic potency of a chemical substance were determined. Auxotrophic strains of *Salmonella typhimurium* G 46 *his*⁻ and *Serratia marcescens* a 21 *leu*⁻ served as the test organisms. Hydrazine sulphate with an LD₅₀ on sc administration of > 2000 mg/kg and isonicotinic acid hydrazide with an LD₅₀ on sc administration of 256 mg/kg were the test substances. Male NMRI/Kisslegg mice each received an ip injection of 2 ml bacterial suspension; the test substance was administered in a single dose. For bacterial counts, 0.2 ml suspension was streaked out on each of at least five plates/animal for both the auxotrophic and reversely mutated bacteria. The survival time after infection with test organisms was investigated by injecting various bacterial dilutions ip into groups of 50 mice and determining the content of auxotrophic and reversely mutated bacteria in the animals at the time of death. Animals were observed for 72 hr in the *Salmonella* experiments and 48 hr in the *Serratia* experiments. The experimental results were analyzed by two methods. The mutation factor calculated from the mutation frequencies and a comparison of linear regression lines describing the population growth of the auxotrophic and test substance-induced mutants during the logarithmic growth phase. The results of these analyses indicated that the following conditions are necessary for a mutagenicity test in which the bacterial content is not only determined at a single time but is also investigated over its temporal course: 1) high bacterial doses must be injected to obtain high bacterial counts, 2) doses of substance must be used that ensure that the experimental animals are not seriously affected toxically during the experiment, and 3) the

procedure should be limited to four hr. The authors conclude that the linear regression analysis for the dynamic mutagenicity test is suitable for routine mutagenicity testing if performed between 0.5 and 4 hr after infection of the mice so that it coincides with the logarithmic growth phase.

- 5509 ABSENCE OF CARCINOGENIC ACTIVITY IN BD RATS AFTER ORAL ADMINISTRATION OF HIGH DOSES OF BISMUTH OXYCHLORIDE. (Eng.) Preussmann, R. (Institut für Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum Heidelberg, D6900 Heidelberg 1, West Germany); Ivankovic, S. *Food Cosmet. Toxicol.* 13(5):543-544; 1975.

Bismuth oxychloride (BiOCl), a pearlescent white pigment used as a coloring agent in cosmetics, was administered to 40 male and female BD rats in the diet at concentrations of 1, 2, or 5% for two years. The types and incidence of tumors observed in surviving rats after their natural death were compared with those in 60 untreated controls. No macroscopic or histologic findings could be attributed to BiOCl treatment. The five mammary fibroadenomas and one hypophyseal adenoma observed in the treated rats were spontaneous tumors characteristic of the BD strain. Control rats developed a total of five tumors including one mammary carcinoma, two mammary fibroadenomas, and two hypophyseal adenomas. The mean body weight of the test groups did not differ significantly from that of the controls, and the mean survival times of the treated groups also corresponded with those of the controls. It is concluded that BiOCl is noncarcinogenic in rats after po administration even at high levels (1,750 g/kg in males).

- 5510 COLONY INHIBITION MEDIATED BY NONIMMUNE LEUKOCYTES *IN VITRO* AND SKIN REACTIVITY *IN VIVO* AS INDICES OF TUMORIGENICITY OF GUINEA PIG CULTURES TRANSFORMED BY CHEMICAL CARCINOGENS. (Eng.) Evans, C. H. (Natl. Cancer Inst., Bethesda, Md.); Cooney, A. M.; DiPaolo, J. A. *Cancer Res.* 35(4):1045-1052; 1975.

Two short-term assays that differentiate tumorigenic cells (transformed *in vitro* by a chemical carcinogen) from nontumorigenic cells are described. One assay measures inhibition of colony growth mediated by nonimmune leukocytes. The other measures skin reactivities on nonimmunized syngeneic guinea pigs. Cells were obtained from inbred strain 2 guinea pig fetuses from the NIH colony. Mineral oil-induced peritoneal exudate (PE) cells were obtained from healthy nonimmunized syngeneic guinea pigs. PE cells were cultured for 24 hr. Culture medium with the nonadherent cells was incubated with tumorigenic or nontumorigenic target cells in ratios of 1000/1 to 10/1. Fewer target cell colonies were observed in the cultures with tumorigenic than nontumorigenic cells after incubation for 7-9 days in the presence of PE cell culture (PEC). Tumorigenic cell inhibition was dependent on PEC concentration; a 100% decrease in colony size and as much as an 80% decrease in the number of colonies were noted at the 1000/1 PEC/-

target cell ratio. Inhibitory activity was present primarily in the supernatant of the PE cells' culture medium. Phytohemagglutinin stimulation of PE cells increased PEC and PEC medium supernatant colony-inhibitory activity as much as 2-fold. In the second assay, two or five million tumorigenic or nontumorigenic cells were inoculated intradermally into 12 to 16 week-old male nonimmunized syngeneic guinea pigs. After four days, skin reactivities were measured. The degree and persistence of induction was greater to tumorigenic cells than nontumorigenic cells. In both assays, tumor-producing cells, transformed in culture, or tumor-derived cells, were affected more than early-passage-untreated fetal cells, morphologically non-transformed long-term-cultured cells previously exposed to noncarcinogenic chemicals, or chemical carcinogen-transformed but non-tumor-producing cells. The nonimmune leukocyte-mediated colony inhibition provides a greater degree of discrimination. The two assays provide rapid estimation of tumorigenic potential of cells transformed in an *in vitro* model system of chemical carcinogens.

- 5511 ALTERATION OF INDUCED CELLULAR AND HUMORAL IMMUNE RESPONSES BY PESTICIDES AND CHEMICALS OF ENVIRONMENTAL CONCERN: QUANTITATIVE STUDIES OF IMMUNOSUPPRESSION BY DDT, AROCLOR 1254, CARBARYL, CARBOFURAN, AND METHYLPARATHION. (Eng.) Street, J. C. (Toxicology Program, Utah State Univ., Logan, Utah 84322); Sharma, R. P. *Toxicol. Appl. Pharmacol.* 32(3):587-602; 1975.

Dose-dependent, immunosuppressive effects of continued dietary treatment of rabbits with 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane (DDT), Aroclor 125 (mixed chlorinated biphenyls averaging 54% chlorine), 1-naphthyl-N-methylcarbamate (carbaryl), 2,2-dimethyl-2,3-dihydrobenzofuronyl-7-N-methyl carbamate (carbofuran), and O,O-dimethyl-O-4-nitrophenyl thiophosphate (methylparathion) was studied. Male white New Zealand rabbits were given a diet containing graded amounts of chemicals for four weeks and challenged with SRBC and Freund's adjuvant. The testing followed for an additional four weeks while the animals were maintained on the same diets as before. The most sensitive indication of immunosuppression was based on evaluation of lymphatic organs, primarily those dependent on thymus-derived lymphocytes. The chemical treatments resulted in a decreased count of plasma cells in popliteal lymph nodes (except with carbaryl), reduction of germinal centers in the spleen, and increasing atrophy of thymus cortex. These responses were generally scaled to increasing levels of the compounds tested. Hemolysin and hemagglutinin titers were not significantly affected by any of the chemical treatments nor were consistent trends observed. The antigen-induced increase in serum γ -globulin was consistently decreased with DDT, Aroclor, carbaryl, and carbofuran treatments, but only carbaryl produced significant changes (at ten days postantigen). DDT groups showed significantly higher preantigen γ -globulin values that were less evident following antigen challenge. Skin sensitivity to tuberculin was decreased (except with carbaryl) but generally only at high dosages of the

test chemicals. None of the compounds showed any effect on growth, food consumption, WBC count, or on organ-to-body-weight ratios for liver, kidney, spleen, and adrenal, except for slight liver enlargement caused by Aroclor 1254. Testing of general effects upon immune responses is important in relation to health aspects of pesticides or other environmental chemicals.

- 5512 LOWERING EFFECT OF CARBON TETRACHLORIDE ON MICROSOMAL CYTOCHROME P-450 OF RAT LIVER. (Eng.) Ota, M. (Iwate Medical Univ. Sch. Medicine, Morioka, Iwate, Japan); Sato, N.; Uemura, H.; Obara, K. *Chem. Biol. Interact.* 11(4):265-276; 1975.

The lowering effect of CCl_4 on the amount of hepatic microsomal cytochrome P-450 of male Wistar rats was studied *in vitro*. CCl_4 (5-20 μl), added directly into the media containing microsomal suspensions, decreased the amount of cytochrome P-450 detectable by difference spectra at zero time of incubation. The incubation of the media with CCl_4 at 37 C in an open system or in a closed system did not decrease the content of cytochrome P-450. Cytochrome P-420 was not detected with CCl_4 at < 10 $\mu\text{l}/5\text{ ml}$. The activity of NADPH-cytochrome *c* reductase was not affected by CCl_4 . The results indicate that the CCl_4 -induced decrease of the amount of detectable cytochrome P-450 is due to the destruction of cytochrome P-450; the binding of cytochrome P-450 to CCl_4 so that it was not detected by the assay; and to the conversion of cytochrome P-450 to P-420.

- 5513 METABOLISM OF INTRAVENOUSLY INJECTED CADMIUM-BINDING PROTEIN. (Eng.) Cherian, M. G. (Univ. Western Ontario Medical Center, London, Ontario, Canada); Shaikh, Z. A. *Biochem. Biophys. Res. Commun.* 65(3):863-869; 1975.

The role of metallothionein in the transport of cadmium is explored. Female Sprague-Dawley rats were used as test animals. Synthesis of metallothionein was induced by sc injection of 10 μM CdCl_2/kg at 24 hr intervals for five days. To label the protein with ^{109}Cd , the injection solution contained carrier-free ^{109}Cd , while labeling with ^{14}C or ^{35}S was accomplished by the simultaneous daily ip injection of 20 μCi of radiolabeled cystine solution and CdCl_2 . Metallothionein from liver tissue was isolated and the protein contents were estimated by atomic absorption and calorimetric procedure. In other experiments, rats were anesthetized, and labeled metallothionein of $^{109}\text{CdCl}_2$ was injected through a cannulated jugular vein at various levels. Bile and urine samples were collected while the rats were under anesthesia. When these rats were sacrificed, liver, kidney, pancreas, and spleen were homogenized, and prepared in 0.25 M sucrose for counting. Kidney supernatant and urine samples were chromatographed on a 0.9 x 60 cm calibrated Sephadex G-75 column. The elution was monitored at 254 nm. ^{109}Cd was counted in a well-type Packard gamma spectrometer equipped with an NaI

crystal, and a Packard liquid scintillation spectrometer was used to measure ^{14}C and ^{35}S radioactivity. More than half the injected $^{109}\text{CdCl}_2$ was accumulated in the liver within three hr (103.40 μg). Comparable doses of metallothionein resulted in a lower liver deposit (32.4 μg). Only a small amount of ^{109}Cd was accumulated in the kidney (3.0 μg) with a 200 μg injected dose. Cadmium in urine excretions after administration of CdCl_2 was not significant, although large amounts of ^{109}Cd injected as metallothionein was excreted in the urine. The deposit of ^{109}Cd injected in any form in pancreas and spleen was small. Kidneys took up significant amounts of ^{109}Cd and ^{35}S from injected metallothionein. Fractionation of kidney supernatants showed that about 85% of supernatant ^{109}Cd was bound to metallothionein; however, in the kidney supernatant of a rat injected with [^{35}S]-metallothionein only 40% of the supernatant radioactivity was recovered. Fractionation of urine samples of rats injected with ^{109}Cd , ^{14}C or ^{35}S labeled metallothionein on Sephadex showed that the major recovered radioactivity was in the metallothionein elution region.

- 5514 CARCINOGENICITY IN MICE OF SOME FATTY AND METHYL ESTERS. 2. PERORAL AND SUBCUTANEOUS APPLICATION. (Eng.) Kiaver, H. W. (Patologisk Institut, Aalborg sygehus Nord, Postbox 561, DK-9100 Aalborg, Denmark); Glavind, J.; Arffmann*, E. *Acta Pathol. Microbiol. Scand.* [A] 83(5):550-558; 1975.

Two fatty acid methyl esters, methyl oleate (MO) and methyl-12-oxo-*trans*-10-octadecenoate (MOO), were tested for carcinogenicity by po and sc administration in male and female ST/a mice. In the experiments with po administration, MO or MOO (each 15 mg/day) was given in the diet for 300 days to previously untreated mice or to mice initially given 4-nitroquinoline 1-oxide (NQO, 1.1 mg) by stomach tube. In the other experiments, the mice received weekly sc injections of MO or MOO (equal to total doses of 0.185 or 0.025 ml) with or without previous topical application of 7,12-dimethylbenz[*a*]anthracene (DMBA, 50 μg). Four of 19 mice surviving 57 wk after NQO treatment alone developed a papilloma in the forestomach. Given in the diet, MOO increased the incidence of forestomach papillomas within 83 wk after initiation by NQO; the percentage of papilloma-bearing mice as well as the number of forestomach papillomas per animal was twice that seen in mice treated with NQO alone. Ingestion of MO increased the total number of papillomas, but not the relative number of tumor-bearing mice. The incidence of skin papillomas after DMBA application was not increased by the subsequent sc injections of methyl esters. The latency period was, however, lowered in mice injected with MO and, especially, with MOO in the higher total dose. Five weekly injections of MOO (0.025 ml) induced two local sarcomas in 20 female mice initiated with DMBA. In no other animals did sarcomas appear at the injection site within a 2-yr observation period. An influence of the injected methyl esters on initiated skin carcinogenesis is possible, though presumably weak. However, the results of the feeding experiments suggest a promoting potency of MOO in

gastric carcinogenesis. Thus, more extensive studies should be conducted to determine the human hazard involved in dietary intake of oxygen-containing derivatives of oleic acid.

- 5515 EFFECT OF METHYLXANTHINES ON HEPATIC MICROSOMAL ENZYMES IN THE RAT. (Eng.) Aeschbacher, H.-U. (Nestle Products Technical Assistance Co. Ltd., Biological Lab., 1350 Orbe, Switzerland); Wurzner, H.-P. *Toxicol. Appl. Pharmacol.* 33(3): 575-581; 1975.

Because of the considerable consumption by man of methylxanthine-containing beverages and drugs, investigations on the possible interaction between methylxanthines and their effect on the hepatic microsomal enzyme system were carried out. Four groups of 12 male outbred Charles River (CD) male rats were given one of three methylxanthines (caffeine, theophylline, or theobromine) separately or in combination. Pretreatment with these substances lasted either three days, when rats were given high doses of methylxanthines (150 mg/kg/day), or six days when the lower doses (37.5 mg/kg/day) were administered. Aniline hydroxylation and *p*-nitro anisol and aminopyrine demethylation were induced when methylxanthines were given at high dose but remained unchanged when the lower dose was administered. Microsomal enzyme activity was dependent on the length of treatment and on the time of the determination (3, 12, and 48 hr) after the last administration; pretreatment during the 6-day period resulted in maximal activity 12 hr after administration, while maximal activity occurred at 48 hr when the treatment lasted only three days. Liver protein synthesis was not influenced by the action of methylxanthines. The results show that the same concentrations of methylxanthines present in tea or coffee do not change the *in vitro* microsomal enzyme activity in rats and are thus thought not to exert an effect on these enzyme activities in man.

- 5516 INDUCTION OF THE POLYAMINE-BIOSYNTHETIC ENZYMES IN MOUSE EPIDERMIS AND THEIR SPECIFICITY FOR TUMOR PROMOTION. (Eng.) O'Brien, T. G. (Univ. Wisconsin Medical Center, Madison, Wis. 53706); Simsiman, R. C.; Boutwell, R. K. *Cancer Res.* 35(9):2426-2433; 1975.

The induction of ornithine decarboxylase and *S*-adenosyl-L-methionine decarboxylase in mouse epidermis by various classes of tumor-promoting and nonpromoting compounds was studied to determine the specificity of this response for tumor promotion. In experiments involving a single topical application of the compounds tested, groups of four female Charles River CD-1 mice were treated with 0.2 ml of one of the compounds dissolved in acetone (17 nM of phorbol didecanoate, phorbol dibenzoate, and phorbol diacetate; 10 μ M iodoacetic acid; 2.2 μ M anthralin; 100 mg Tween 60; 0.04 mM ethyl phenylpropionate; 50 μ g cantharidin; 15 mg acetic acid; and 0.1 or 3.6 μ M 7,12-dimethylbenz(*a*)anthracene) and killed at various periods up to 48 hr. In studies of the effects of multiple applications of the test compounds

groups of 24 mice were treated at 3- to 4-day intervals with 0.2 ml of one of the compounds dissolved in acetone (1 μ M iodoacetic acid, 2.2 μ M anthralin, 100 mg Tween, 17 nM 12-*O*-tetradecanoyl-phorbol-13-acetate), and groups of four mice were killed at various times up to 48 hr. Following homogenization of the epidermis of 4-5 mice and centrifugation at 30,000 $\times g$ for 30 min at 0 C, the supernatants were used for estimation of enzyme activity. Enzyme activity rapidly increased after treatment with the active promoters, reaching a peak (50-fold greater than control after phorbol didecanoate treatment, 20-fold greater than control after phorbol dibenzoate) 4-5 hr after application, and returning to the control level by 12 hr, where it remained for up to seven days. Iodoacetic acid, anthralin, and Tween 60 (all promoting compounds) also stimulated both of these enzyme activities after single and multiple applications. The hyperplastic agents acetic acid, cantharidin, and ethyl phenylpropionate had little effect on ornithine decarboxylase activity, but did have a pronounced effect on epidermal *S*-adenosyl-L-methionine decarboxylase activity (the activity gradually increased to a peak 3- to 5-fold greater than control at 15 hr and declined to near control levels by 48 hr). Enzyme activities were also stimulated two days after a single application of 3.6 μ M of 7,12-dimethylbenz(*a*)anthracene (a carcinogenic dose), while no response at any time was observed after 0.1 μ M. It is concluded that the induction of ornithine decarboxylase in mouse epidermis is one of the earliest and largest effects of tumor promoters, and that there is a good correlation between *S*-adenosyl-L-methionine decarboxylase activity and hyperplasia.

- 5517 PROPERTIES OF CELLS FROM DIFFERENT SPECIES ACCOMPANYING CHEMICAL CARCINOGEN INDUCED TRANSITION TO THE NEOPLASTIC STATE. (Eng.) Evans, C. H. (Nat'l. Cancer Inst., Bethesda, Md.); DiPaolo, J. A. *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 118-121.

A rapid, quantitative method for identifying neoplastic cells, transformed in a cell culture by carcinogens, is described. The method is a colony inhibition assay using leukocytes from unimmunized guinea pigs. Initially, cells from guinea pig or hamster fetuses were exposed to the potentially carcinogenic chemical (1) in utero by ip injection of pregnant animal prior to excision of fetus (2) by treatment of secondary mass cell culture for five days. If chemical was carcinogenic, cellular alterations were seen as early as seven days after treatment. Morphological transformation of the cells occurred in two-thirds of the altered cell cultures, however tumorigenicity coincided with transformation in only two-thirds of the cultures studied for six months. Tumorigenicity was defined as the ability to produce tumors in newborn syngeneic guinea pigs irradiated with 450 rads of Cobalt 60 the day prior to injection of cells. Agar colony growth proved to be the only growth parameter of

several studied, e.g. plating efficiency, saturation density, population doubling time, and chromosome number, that consistently correlated with tumorigenicity. Agar colony growth inhibition was assayed by inoculation of petri dishes with mixtures of 100-200 target cells and cultured, centrifuged cells from peritoneal exudate (PE) obtained from syngeneic unimmunized guinea pigs or mixtures of target cells and PE cell culture supernatant medium. After incubation for seven to nine days, the number of colonies greater than 0.2 mm in diameter were counted. The number of colonies formed by tumorigenic cells was reduced 10-17% and 45-53% by PE cell culture medium (PES) in dilutions of 1/100 and 1/10, resp. PES had an inhibitory effect of less than 10% on nontumorigenic cell colony formation, and in some instances, the effect was stimulatory. It is evident that the cytotoxic effect of PES can provide a rapid method of identifying neoplastic cells from mammalian cell systems exposed to carcinogens.

- 5518 EFFECT OF PHARMACOLOGICAL AGENTS ON HUMAN KERATINOCYTE MITOSIS IN VITRO: II. INHIBITION BY CATECHOLAMINES. (Eng.) Harper, R. A. (Skin and Cancer Hosp. Philadelphia, 3322 North Broad St., Philadelphia, Pa. 19140); Flaxman, B. A. *J. Cell. Physiol.* 86(2/Suppl. 1/Part I): 293-299; 1975.

The effects of various catecholamines on human keratinocyte mitosis *in vitro* were studied. Skin explants obtained at surgery were grown in Eagle's minimum essential medium containing 10% fetal calf serum, and the cells were allowed to propagate for 7-10 days at 37 C in a high humidity incubator. Each amine was then added along with colcemid (3.5 µg/ml) for four hours before the number of arrested metaphases was determined. Epinephrine produced significant mitotic inhibition (49%) at a concentration as low as 4.5×10^{-10} M, while its analog, isoproterenol, produced 47% inhibition at 1×10^{-10} M. Norepinephrine elicited a 49% inhibitory response at 1×10^{-8} M. Dopamine, caused a 53% decrease in mitosis at 1×10^{-6} M. Other structurally related amines that exhibited mitotic inhibition were phenylephrine, 58% at 1×10^{-7} M; octopamine, 47% at 1×10^{-5} M; and tyramine, 52% at 1×10^{-4} M. Serotonin showed no mitotic inhibition at 1×10^{-4} M. Various α and β adrenergic blocking agents were added to the cell system one-half hour before the addition of amine and calcemid. The α blocking agent, phentolamine, had no effect on mitosis. When added in conjunction with epinephrine or norepinephrine, no reduction of the catecholamine-induced mitotic inhibition was observed. The β blocking agent, propranolol, by itself showed slight mitotic inhibition at 1×10^{-6} M. When added along with epinephrine or norepinephrine, propranolol reduced the catecholamine-induced mitotic inhibition approximately 65%. In addition, propranolol blocked mitotic inhibition caused by phenylephrine, an α adrenergic agent. However, another β blocking agent, dichloroisoproterenol, showed strong mitotic inhibition (53%) when added alone to the cultures at a concentration of 1×10^{-8} M. The effect was reduced to zero in the presence of pro-

pranolol. These data suggest that while β receptors may be involved in the catecholamine-induced mitotic inhibition of human keratinocytes *in vitro*, the nature of the receptor-molecule interaction may be complex.

- 5519 COLCEMID-INDUCED CHROMOSOMAL NON-DISJUNCTION IN NORMAL AND TRANSFORMED MAMMALIAN CELLS *IN VITRO*. (Rus.) Kopnin, B. P. (Inst. of Experimental and Clinical Oncology, Acad. of Medical Sciences of the U.S.S.R., Moscow, U.S.S.R.); Stavrovskaya, A. A. *Genetika* 11(2):118-124; 1975.
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See also:

- * (Rev): 5401, 5402, 5403, 5405, 5406, 5407, 5413, 5427, 5430, 5431, 5432, 5433, 5434, 5435, 5440, 5441
- * (Viral): 5634
- * (Immun): 5671, 5681, 5682, 5703, 5710, 5720, 5744, 5758, 5764
- * (Path): 5773, 5783, 5790, 5799
- * (Epid-Biom): 5865, 5867, 5868, 5869, 5870, 5871, 5883

- 5596 RECOVERY FROM RADIATION-INDUCED DECREASE IN CELL MEMBRANE CHARGE BY ADENOSINE TRIPHOSPHATE AND ITS MODIFICATION BY COLCHICINE OR CYTOCHALASIN B. (Eng.) Sato, C. (Aichi Cancer Center Inst., Chikusa-ku, Nagoya 464, Japan); Kojima, K.; Nishizawa, K. *Biochem. Biophys. Res. Commun.* 67(1):22-27; 1975.

To test the hypothesis that ATP-dependent polymerizing proteins might be involved in conformation change of the cell membrane, the effect of ATP in the presence and absence of colchicine or cytochalasin B were investigated. Wistar King A rat RBC were X-irradiated; after subsequent centrifugation, the electrophoretic mobility of individual cells was measured at 25 C. Cell electrophoretic mobility of the RBC decreased with time after 3000 R X-irradiation without spontaneous recovery. On addition of 10^{-4} M ATP to the irradiated cells, recovery was observed within ten minutes. Washing out of ATP and subsequent incubation for one hour resulted in the return of mobility to the low level. Preincubation with 0.1 μ g/ml colchicine for 15 min or 1 μ g/ml cytochalasin B for 30 min completely blocked the reversible effect of ATP on electrophoretic mobility. These results suggest the existence of tubulin-like polymerizing protein in the cytoplasmic membrane and changes in its conformation induced both by X-irradiation and by added ATP.

- 5597 THYROID CELL PROLIFERATION IN RATS AND INDUCTION OF TUMORS BY X-RAYS. (Eng.) Christov, K. (Natl. Center of Oncology, Acad. Medicine, Plovdivsko pole 6, Sofia-56/Darvenitza, Bulgaria). *Cancer Res.* 35(5):1256-1262; 1975.

The effect of X-irradiation of the neck (300 rads) on the induction of thyroid tumors was studied in male Wistar rats irradiated before or during thyroid cell proliferation induced by 4-methyl-2-thiouracil (MTU, 0.1% in drinking water). Measurements of the 3 H-thymidine labeling index and the mitotic index showed there were very few proliferating cells in the thyroid gland of normal adult rats. MTU induced an exponential increase of thyroid weight after a lag phase of two days; the increase continued for eight days and was followed by a plateau phase. The following sequence of events was found for the number of dividing follicular and stroma cell as well as for DNA synthesis; no significant changes during the 1st two days, a sharp increase between the second and eighth days, a decrease between the eighth and 14th days, and an almost constant flow until the 24th day. X-rays given to a nonproliferating thyroid gland induced tumor growth in 25% of 20 animals 18 mo after irradiation. The same dose of irradiation, applied to a proliferating thyroid gland, increased the tumor incidence to 30% when administered in the lag phase, to 75% when administered at the peak of the proliferating phase, and to 62.5% when administered at the plateau phase. Subsequent treatment of irradiated animals with MTU enhanced the number and the size of the thyroid tumors and led to the occurrence of more carcinomas than appeared in animals treated with X-rays only or MTU only. The tumors induced by treatment with

X-rays and MTU were predominantly follicular or papillary adenomas and carcinomas. A synergistic effect was evident since the number of tumors produced by the combination of both treatments was higher than the sum of their individual effects.

- 5598 EFFECT OF RADIOPHOSPHORUS ON HEMATOLOGY OF MICE DURING POSTNATAL DEVELOPMENT. (Eng.) Malhotra, N. (Sch. Life Sciences, Jawaharlal Nehru Univ., New Delhi 110057, India); Srivastava*, P. N. *Strahlentherapie* 150(4):411-426; 1975.

The effect of radiophosphorus on the hematology of mice during postnatal development was investigated. Swiss Albino mice at different stages of their postnatal development (1-day, 1-wk, 2-wk, 3-wk, 4-wk age groups) were injected ip with radioactive phosphorus (P-32) (1.0 μ Ci/g) and studied for their hematological response at weekly intervals up to sexual maturity. In all the treated groups the radiation injury was evident in both males and females (six weeks). Animals showed reduction in RBC and WBC numbers and a fall in hemoglobin and hematocrit levels after injection. Reparation was also evident in the animals after some lapse of time following P-32 administration. Morphological changes in different WBC were not observed. No radiation sickness symptoms were observed in any of the treated groups. There were no deaths due to radiation. The radiation damage to blood forming organs was moderate. Females showed a greater hematological damage than the males. Damage to hematopoietic organs at this dosage of radioactive phosphorus is apparently moderate, as evidenced by the late appearance of symptoms in the peripheral blood.

- 5599 CHROMATID AND HALF-CHROMATID ABERRATIONS IN CHINESE HAMSTER CELLS X-IRRADIATED IN METAPHASE, PROPHASE, OR G₂. (Eng.) Dewey, W. C. (Dept. Radiology and Radiation Biology, Colorado State Univ., Fort Collins, Colo.). *Cell Cycle in Malign. Immun., Proc. Annu. Hanford Biol. Symp.*, 13th. Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 182-192.

The types and frequencies of chromosomal aberrations were studied both in Chinese hamster ovary cells not delayed in their cycle by X-irradiation, i.e., located beyond an X-marker existing ten minutes prior to prophase, and in cells delayed by irradiation, i.e., located in G₂ prior to the X-marker. Cells located beyond the X-marker at the time of irradiation, i.e., cells in metaphase, prophase, and in late G₂ within ten minutes of prophase, were physically separated from cells located prior to the X-marker by mitotic selection to collect the cells as they entered metaphase and anaphase. These mitotic cells were fixed immediately or were allowed to traverse one cell cycle before they were fixed. When cells reached their first metaphase following irradiation, those irradiated prior to the X-marker manifested chromatid deletions and exchanges, but those irradiated beyond the X-marker sustained no

visible aberrations. However, when prophase and metaphase cells were treated with Colcemid (0.06 $\mu\text{g/ml}$) for 60 min following irradiation, gaps and chromatid deletions appeared. Thus, in cells located beyond the X-marker, there was neither division delay nor evidence of aberrations. Only when a delay was artificially produced with Colcemid did aberrations begin to appear. When cells reached their second metaphase following irradiation, both those prior to and beyond the X-marker at the time of irradiation sustained only chromosome deletions and exchanges. This finding contrasts with a previous observation of a high frequency of chromatid type deletions and exchanges in cells X-irradiated in metaphase following a 2-hr treatment with Colcemid and then scored for aberrations in the next metaphase. Thus, true half-chromatid exchanges, which are evidenced by chromatid exchanges in the second metaphase, prophase, or in G_2 prior to the X-marker. However, the bineme nature of the mitotic chromatid can be readily observed in radiation studies if metaphase cells are treated with Colcemid prior to X-irradiation.

- 5600 THE EFFECT OF CONTINUOUS IRRADIATION ON CELL PROLIFERATION AND MATURATION IN SMALL INTESTINAL EPITHELIUM. (Eng.) Rijke, R. P. C. (Dept. Cell Biology Genetics, Erasmus Univ. Rotterdam, P.O. Box 1738, Rotterdam, The Netherlands); Plaisier, H.; Hoogeveen, A. T.; Lamerton, L. F.; Galjaard, H. *Cell Tissue Kinet.* 8(5):441-453; 1975.

During the course of continuous irradiation, the changes in the number of villus cells per column, the proliferative activity in the crypt, and the localization of the proliferative zone was investigated. Male August-Marshall hybrid rats were irradiated with a dose of 290 rads of cesium-137/day for five days, then allowed seven days recovery. Following ip injection of 100 μCi tritiated thymidine ($^3\text{H-TdR}$), segments of the small intestine were removed and processed for dipping autoradiography. Cryostat sections were utilized in scintillation counting and microchemical analyses. The number of cells per crypt column was hardly reduced during continuous irradiation, while the villus length was reduced to approximately 70% of normal. The percentage of labeled crypt cells decreased at day one of irradiation, but was normal during subsequent days. Throughout the irradiation period, there was a decrease in the percentage of labeled cells for those cell positions normally exclusively involved in proliferation. The nonspecific esterase, used as a parameter for crypt cell differentiation, also decreased during irradiation. In contrast, enzymes considered indicators for villus cell function, i.e. alkaline phosphatase, leucine aminopeptidase, and neutral α -glucosidase, remained relatively unaffected. Thus, continuous irradiation effected a slight decrease in the number of cells per crypt column, while the number of cells per villus column remained unchanged. The results were consistent with the hypothesis that an expansion of the proliferative cell compartment in the crypt is determined by changes in the villus cell population.

- 5601 DOMINANT LETHAL MUTATIONS IN MALE MICE FED γ -IRRADIATED DIET. (Eng.) Chauhan P. S. (Bio-Medical Group, Bhabha Atomic Res. Centre Bombay-400 085, India); Aravindakshan, M.; Aiyar, A. S.; Sundaram, K. *Food Cosmet. Toxicol.* 13(4):433-436; 1975.

The possible induction of dominant lethals in male Swiss mice fed an irradiated whole diet was investigated. Three groups of mice were fed a stock ration or an unirradiated or irradiated (2.5 Mrad) test diet for eight weeks. After the feeding period, the males were mated with groups of untreated female mice for four weeks. The females were autopsied at mid-term pregnancy for evaluation of dominant lethal mutations. Numbers of dead implantations including deciduomas and dead embryos showed no significant differences among the different groups, thus producing no evidence of any induced postimplantation lethality in mice fed on the irradiated diet. Similarly, there was no indication of preimplantation lethality, since implantation rates remained comparable among different groups. Consumption of irradiated diet did not affect the fertility of mice. Total pre- and post-implantation loss as indicated by the numbers of live implantations remained comparable among all the groups of mice.

- 5602 FOREIGN-BODY TUMORIGENESIS INDUCED BY GLASS AND SMOOTH AND ROUGH PLASTIC: COMPARATIVE STUDY OF PRENEOPLASTIC EVENTS. (Eng.) Brand, K. G. (Univ. Minnesota Medical Sch., Minneapolis, Minn. 55455); Buoen, L. C.; Brand, I. *J. Natl. Cancer Inst.* 55(2):319-322; 1975.

Foreign-body (FB) tumorigenesis was studied in female CBH/H and CBA/H-T6 mice and their hybrids implanted sc with 0.2-mm thick, large (660-720 mm^2) or small (210-400 mm^2) pieces of glass, smooth-surfaced plastic, or roughened plastic (rigid unplasticized vinyl chloride vinyl acetate copolymer). The tumorigenic process was analyzed in the various implantation groups by the evaluation of tumor incidences and latencies, and by the determination of 1) frequency of originator ("parent") cells, 2) appearance of preneoplastic cells in FB-reactive capsule tissue, 3) expansion of preneoplastic cell clones throughout the tissue capsule, and 4) pace of cellular preneoplastic maturation in terms of time remaining until neoplastic autonomy. Established methods included transfer of preneoplastic FB-reactive tissue capsules to recipient animals (hybrids of CBA/H and CBA/Br or C57BL/10ScSn). Specific preneoplastic events or stages of FB tumorigenesis were affected differently, depending on the size, material, and surface properties of the implants. Small smooth plastic implants produced a lower tumor incidence than large ones due to a lesser frequency of preneoplastic parent cells. Average tumor latency was prolonged. Rough plastic implants did not evoke fewer preneoplastic parent cells than smooth implants of equal size; however, tumor latency was markedly prolonged. Glass implants had a lower tumor incidence than smooth plastic implants of comparable size and therefore

may have evoked fewer preneoplastic parent cells. Furthermore, the appearance of these cells and their clonal expansion were delayed. Tumors induced by large glass *versus* smooth plastic implants did not show the expected difference in average latencies, suggesting that the preneoplastic maturation was not delayed in cells evoked by large glass implants. Despite previous suggestions that vinyl chloride polymers released from plastic may add to the mechanism of FB tumorigenesis, no evidence for chemical cocarcinogenesis was detected in this study.

5603 ON THE ESTIMATION OF ¹⁴C MUTAGENIC EFFICACY. (Rus.) Golenetskii, S. P. (No affiliation given); Suskov, I. I.; Stepanok, V. V. *Radiobiologiya* 15(1):32-36; 1975.

5604 PREVENTION OF SKIN CANCER WITH A PABA IN ALCOHOL SUNSCREEN IN XERODERMA PIGMENTOSUM. (Eng.) Goldstein, N. (Photobiology Res. Lab., 1077 Bishop St., Honolulu, Hawaii 96813); Hay-Roe, V. *Cutis* 15(1):61-64; 1975.

5605 THEORY OF MISREPAIR MUTAGENESIS. (Eng.) Bresler, S. E. (Leningrad Inst. Nuclear Physics, Acad. Sciences U.S.S.R., Leningrad, U.S.S.R.). *Mutat. Res.* 29(3):467-472; 1975.

5606 THE INFLUENCE OF A CHRONIC ENVIRONMENTAL STRESS ON RADIATION CARCINOGENESIS [abstract]. (Eng.) Baker, D. G. (Mt. Zion Hosp. Med. Cent., San Francisco, Calif.); Jahn, A.; Hollander, C. F. *Proc. Am. Assoc. Cancer Res.* 16:55; 1975.

5607 AN IMPROVED APPARATUS FOR SINGLE INHALATION EXPOSURE OF MINIATURE SWINES TO RADIOACTIVE AEROSOLS. (Ger.) Pusch, W. M. (Forschungszentrum der OSGAE, Vienna, Austria). *Atomkernenergie* 26(2): 125-128; 1975.

See also:

- * (Rev): 5401, 5404, 5435, 5443, 5444
- * (Chem): 5491, 5505
- * (Immun): 5696
- * (Epid-Biom): 5868, 5870, 5882

- 5608 EFFECT OF ADENO-ASSOCIATED VIRUS ON CANCER EXPRESSION BY HERPESVIRUS-TRANSFORMED HAMSTER CELLS. (Eng.) Cukor, G. (Boston Univ. Sch. Medicine, Boston, Mass. 02118); Blacklow, N. R.; Kibrick, S.; Swan, I. C. *J. Natl. Cancer Inst.* 55 (4):957-959; 1975.

Experiments were carried out to determine whether infection with adeno-associated virus (AAV) would have a specific effect on the oncogenic potential of a hamster cell line (33-8-9) transformed by herpes simplex virus type 2 (HSV-2). In Lakeview Syrian hamster inoculated sc with 5×10^2 HSV-2-transformed 33-8-9 cells and checked daily for the appearance of palpable tumors, the mean tumor latency (MTL) period was 26.7 days. However, if the cells were first infected with an AAV preparation from which infectious adenovirus had been heat inactivated, the MTL of animals receiving the same 5×10^2 inoculum was 49.8 days. Doubling the inoculum to 1×10^3 cells resulted in an MTL of 20.1 days in control animals and 51.3 days in animals receiving AAV. The survival time of animals injected with AAV tumor cells was also significantly increased (122.5 versus 82.5 days). Treatment of 33-8-9 cells with an AAV-free heated adenovirus preparation had no significant effect on tumor latency. The effect of AAV was specific for HSV-2-transformed hamster cells, since the preparation did not significantly alter the tumor latency period in two hamster tumor cells lines transformed by simian virus 40. It is suggested that AAV antigens, expressed on the surface of infected tumor cells with the aid of HSV-2, may serve as a target for an increased immune response by the host. Alternatively, the interaction of AAV with HSV-2 genetic material in the transformed cell might make the cell less oncogenic.

- 5609 ADENOVIRUS TRANSCRIPTION: II. RNA SEQUENCES COMPLEMENTARY TO SIMIAN VIRUS 40 AND ADENOVIRUS 2 DNA IN Ad2⁺ND₁ AND Ad2⁺ND₃ INFECTED CELLS. (Eng.) Flint, S. J. (Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, Mass. 02139); Wewerka-Lutz, Y.; Levine, A. S.; Sambrook, J.; Sharp, P. A. *J. Virol.* 16(3):662-673; 1975.

The genomes of the two nondefective adenovirus 2/simian virus 40 (Ad2/SV40) hybrid viruses, nondefective Ad2/SV40 hybrid virus 1 (Ad2⁺ND₁) and nondefective hybrid virus 3 (Ad2⁺ND₃), were formed by a deletion of about 5% of Ad2 DNA and insertion of part of the SV40 genome. The cytoplasmic RNA synthesized during both the early and late stages of lytic infection of human cells by these hybrid viruses was compared to that expressed in Ad2-infected and SV40-infected cells. Separated strands of the six fragments of ³²P-labeled Ad2 DNA produced by cleavage with the restriction endonuclease *Eco*RI and the four fragments of ³²P-labeled SV40 DNA produced by cleavage with both *Hpa*I, and *Eco*RI were prepared by electrophoresis of denatured DNA in agarose gels. The fraction of each fragment strand expressed as cytoplasmic RNA was determined by annealing fragmented ³²P-labeled strands to an excess of cellular RNA extracted from infected cells. The segment of Ad2 DNA deleted from both

hybrid virus genomes was transcribed into cytoplasmic messenger RNA during the early phase of Ad2 infection. Hence, it is suggested that Ad2 codes for at least one "early" gene product which is nonessential for virus growth in cell culture. In both early Ad2⁺ND₁ and Ad2⁺ND₃-infected cells, 1,000 bases of Ad2 DNA adjacent to the integrated SV40 sequences were expressed as cytoplasmic RNA, but were not similarly expressed in early Ad2-infected cells. The 3' termini of this early hybrid virus RNA mapped in the vicinity of 0.18 on the conventional SV40 map and probably terminated at the same position as early lytic SV40 cytoplasmic RNA. Therefore, the base sequence in this region of SV40 DNA specifies the 3' termini of early messenger RNA present in both hybrid virus and SV40-infected cells.

- 5610 SYNTHESIS, SURFACE DEPOSITION, AND SECRETION OF IMMUNOGLOBULINS BY ABELSON VIRUS-TRANSFORMED LYMPHOSARCOMA CELL LINES. (Eng.) Premkumar, E. (Microbiological Associates, 4733 Bethesda Ave., Bethesda, Md. 20014); Potter, M.; Singer, P. A.; Sklar, M. D. *Cell* 6(2):149-159; 1975.

To determine whether the theta antigen-negative lymphomas induced in BALB/c mice by injection with Abelson murine type C virus as newborns might be derived from precursors of B lymphocytes, a study was made of immunoglobulin synthesis by three different cultured cell lines established from such tumors. A spontaneous lymphoma cell line, P1798, strongly positive for theta antigen and known to have originated from T cells, was studied as a control. Radioactive iodination of cell membrane proteins was accomplished using intact cells. After being labeled, the cells were lysed with 1% NP 40 and were then processed for isolation of immunoglobulin. In most of the experiments, before the isolation of the immunoglobulins, a heterologous precipitation using ovalbumin and antiovalbumin was carried out in the cell lysates or culture media to remove immunoglobulin-binding proteins. The supernatants from such precipitates were treated with rabbit antisera to mouse IgM, IgG, and IgA and with carrier mouse IgM, IgG, and IgA, and the resulting precipitates, following dispersion in 2% SDS-6 M urea, were subjected to analysis by polyacrylamide gel electrophoresis. Distribution of immunoglobulin fractions in the gels was determined by measurements of radioactivity. It was found that two of the cell lines synthesized monomeric IgM molecules which were deposited in the cell membranes, presumably to serve as antigen receptors. The third cell line was found to synthesize cellular IgG molecules as well as membrane-associated IgM. In addition, the cell lines synthesized a membrane-associated immunoglobulin-detaining protein (MAID), with a molecular wt of 35,000. It was speculated that MAID might play a role in adapting the receptor immunoglobulin molecule to the hydrophobic environment of the cell membrane. The kinetics of amino acid incorporation into immunoglobulins by the cell lines was studied with exponentially growing cells cultured in the presence of ³⁵S-methionine.

The results showed that the lines produced immunoglobulins at a rate which was two orders of magnitude smaller than MOPC 104E plasmacytoma cells. The findings suggest that Abelson virus transforms thymus-independent lymphocytes in various stages of maturation and that these lymphocytes may be of B cell origin. The P1798 T cell lymphoma used as the control was found occasionally to produce minute amounts of immunoglobulin.

5611 ISOLATION OF TWO SUBGROUP-SPECIFIC LEUKEMOGENIC VIRUSES FROM STANDARD AVIAN MYELOBLASTOSIS VIRUS. (Eng.) Ishizaki, R. (Duke Univ. Med. Cent., Durham, N.C.); Langlois, A. J.; Bolognesi, D. P. *J. Virol.* 15(4):906-912; 1975.

The leukemogenic potential of the BAI-A strain of avian myeloblastosis virus (AMV) was investigated *in vivo* using selected genetically defined chicks. Cultures were made from cells obtained from chicken embryos resistant to subgroup E virus and lacking chicken virus group-specific antigen and chick helper factor (chf). Fertile Japanese quail eggs were used for assay of Rous sarcoma virus. Leukemogenicity was determined in selective resistant chicks. The standard AMV was inoculated iv in 3-day-old chicks (5×10^{10} particles/bird). Examination of the hematological characteristics of the blood smears during the first two weeks postinoculation showed myeloblastosis-positive chickens in 9 of 13 C/E, 5 of 8 C/AE, 7 of 9 C/BE, and none of 5 C/ABE chicks. All C/E, C/AE, and C/BE chickens were dead three weeks after inoculation, whereas all C/ABE chicks survived. Attempts were made to isolate subgroup A or B AMV from the standard strain by passage through selected resistant chicks. Five successive leukemia inductions were carried out. A homogeneous subgroup B virus present in plasma was passaged successfully several times in C/AE chicks from line 7 and resulted in the induction of the typical myeloblastic leukemia 2-3 wk after virus inoculation. AMV-A induced myeloblastosis in C/BE and C/E chicks, but not in C/AE or C/AB; AMV-B was active in C/AE but not in C/BE chicks. Analysis of the nonleukemogenic agents present in the isolates was also carried out by standard *in vitro* assays including host range, interfering activity, and neutralization by specific antisera. The nonleukemogenic counterparts in the AMV-A and AMV-B isolates were homogeneous with respect to subgroup. These results indicate that both subgroup A and B isolates of the avian myeloblastosis virus have leukemogenic potential.

5612 ADENOVIRUS BINDS TO RAT BRAIN MICROTUBULES *IN VITRO*. (Eng.) Luftig, R. B. (Worcester Foundation for Experimental Biology, Shrewsbury, Mass. 01545); Weihing, R. R. *J. Virol.* 16(3):696-706; 1975.

Studies were undertaken to determine the possible role of cytoplasmic microtubules in the transport of genetic material from the inner edge of the cell membrane to the nucleus, which must occur for adenovirus to replicate in the nucleus. By negative staining electron microscopy, it was found that

when similar concentrations of adenovirus type 5 and reovirus (viruses of about the same diameter, 75-80 nm, and density, 1.34-1.36 g/cm³) were incubated with a carbon support film containing rat brain microtubules, 72% of adenovirus on the grid, but only 32% (equivalent to random association) of reovirus, were associated with microtubules. Similar concentrations of both larger and smaller particles, such as polystyrene latex spheres and coliphage f2, also exhibited a low degree of interaction, *viz.*, 17-37%, with microtubules. Moreover, 90% of microtubule-associated adenovirus bound to within ± 4 nm of the edge of microtubules, but lower fractions (again equivalent to a random association) of the other particles bound to the edge of the microtubules. The mechanism behind this phenomenon, designated "edge binding", is presently obscure; however, it provides a second method to distinguish between the microtubular association of adenovirus and other particles. Edge binding of adenovirus also occurred when adenovirus was initially placed on the carbon support film and then incubated with microtubules and when adenovirus and microtubules were mixed prior to placement on the support. In contrast, reovirus or the other particles prepared by similar techniques exhibited a random amount of edge binding. The binding of adenovirus appears to involve the hexon capsomers of the virion since (a) high resolution electron micrographs showed that the edge of the virus was in contact with the edge of the microtubules, and (b) adenovirions briefly treated with formamide (40%) to remove pentons and fibers bound as efficiently as intact virions. Core structures, which were obtained by further formamide degradation of the virion, did not associate with microtubules. These observations support the hypothesis that the transport of adenovirions within infected cells is mediated by interaction with microtubules.

5613 EVIDENCE FOR A HOST CELL SURFACE ANTIGEN ON THE ENVELOPE OF AVIAN TUMOUR VIRUSES. (Eng.) Aupoix, M. (Unité de Recherches sur les Virus de l'I.N.S.E.R.M., Lyon, France); Vigier, P. *J. Gen. Virol.* 27(2):151-161; 1975.

Chicken sarcoma viruses from five different subgroups were investigated for evidence of a host cell surface antigen on the viral envelope. Undiluted or diluted medium of Rous sarcoma virus-infected cultures containing 10^4 - 10^5 focus forming U/ml was mixed with rabbit anti-chicken embryo cells (CE) or anti-RS2/10 (nonpermissive Rous sarcoma virus-transformed hamster cells) serum and complement, in the ratio 9:1:2, incubated 1 hr at 37 C, diluted 20-fold in standard medium, and assayed for focus formation on secondary cultures of CE cells plated 1 day before. Controls were: 1) virus incubated with the antisera, but without complement; 2) virus incubated with complement, but with normal rabbit serum or minimum essential medium (MEM) instead of the antisera; 3) virus incubated with normal serum and MEM instead of complement; and 4) virus incubated with MEM instead of serum and complement. Assay cultures were infected for 1 hr at 37 C, and the inoculum was removed. The infected cultures were overlaid with

standard medium gelled with agar and incubated at 37 C. They were re-fed by addition of the same medium 7 days later, and foci were scored at 14 days, for Bryan strain Rous sarcoma virus, or at 10 days for other viruses. Viruses from the five different subgroups were inactivated about 100-fold by the rabbit anti-CE serum in the presence, but not in the absence, of complement. The inactivation was not due to the action of the anti-serum and complement on the CE cell cultures used for virus assay, nor to anti-Forssman antibodies, but was probably due to antibodies to some antigen(s) common to the surface of chicken embryo cells and to the virus envelope. This host cell surface antigen was also present on nontransforming viruses as well as on transforming viruses, since the Bryan strain of Rous sarcoma virus which was inactivated to the same degree as Rous sarcoma virus from other strains by anti-CE serum and complement is coated with an envelope borrowed from its nontransforming helper virus. A parallel electron microscopical study revealed a characteristic swelling and loss of opacity to electrons of virus particles treated with the antiserum and complement, which appeared to precede virolysis. The results also indicate that the avian viruses contain no cell neoantigen common to transformed permissive and nonpermissive cells; this is in agreement with earlier findings.

- 5614 DETECTION OF LEUKEMIA VIRUS INFECTION IN TWO LINES OF CHICKENS. (Rus.) Shmel'kova, V. I. (All-Union Scientific Res. Inst. of Rearing and Genetics of Useful Animals, U.S.S.R.); Batrakova, V. P.; Kniazev, P. G.; Perevozchikov, A. P.; Chernina, L. A.; Vieru, E. A.; Sokolova, A. N.; Kuznetsov, O. K. *Veterinariia* (8):35-36; 1975.

Tissue cultures prepared after 9-12-day incubation from 676 embryos of 137 C line chickens, and from 910 embryos of 160 chickens of line 9787 were investigated for leukemia virus infection by the COFAL test. Leukemia virus was detected in 33 of the line C chickens, and in 13 of the line 9787 chickens. Virus particles of type C were found in the positive samples by electron microscopy. Reverse transcriptase, indicative of an oncornavirus type infective agent, was found in the purified virus preparations. Despite virus infection, the animals were clinically normal, and free from leukemic changes. Changes indicative of leukemia were detected in the inner organs in 3 of 30 chickens.

- 5615 CHARACTERIZATION OF A CONDITIONAL MUTANT OF ROUS SARCOMA VIRUS WITH ALTERATIONS IN EARLY AND LATE FUNCTIONS OF CELL TRANSFORMATION. (Eng.) Bookout, J. B. (Texas Medical Center, Houston, Tex. 77025); Sigel, M. M. *Virology* 67(2):474-486; 1975.

Mutants were isolated from γ -irradiated (^{60}Co , 2.5×10^6 R) stocks of Schmidt-Ruppin Rous sarcoma virus (SR-RSV-2). One isolate, MI-100, displayed unusual properties in its temperature sensitivity of

cell-transforming capabilities. Focus formation, colony formation in soft agar, and increased [^3H]-deoxyglucose uptake by infected cells were all rendered temperature sensitive (*ts*); 37 C was permissive for expression of these functions, while 41 C was nonpermissive. Tumorigenicity in Leghorn chickens in the mutants was greatly diminished; 2×10^2 focus forming units (FFU) wild type virus gave a 90% incidence about 7-10 days after injection, while MI-100 gave no tumors. Larger doses (2×10^3 , 2×10^4) caused low tumor incidence at a latent period of at least 17 days. Virus replication was not defective because virus yields exceeded those of wild-type RSV at 37 and 41 C. Yields of infectious progeny may have been higher than shown by titrations, as virions of MI-100 were more heat labile than wild type. Group-specific antigen concentrations in MI-100 infected were almost equivalent at 37 and 41 C and greater at both temperatures than those of wild-type-infected cells. Through genetic recombination with Rous-associated virus (RAV-1), subgroup specificity of MI-100 was altered from B to A without correcting the temperature sensitivity of transformation. However, temperature-shift experiments demonstrated a major difference in the *ts* properties of the mutant and its recombinant. MI-100 was unable to transform cells at 37 C if initial incubation after infection was at 41 C (irreversible inhibition); also, shifts of infected cells, at any time, from 37 to 41 C resulted in loss of the transformed phenotype (reversible inhibition). Cells infected with the recombinant still required permissive temperature in order to express the transformed phenotype, but initial incubation at 41 C after infection did not affect the ability to transform cells at 37 C. Thus there appeared to be *ts* lesions in MI-100 affecting transformation, one in an early function and one related to a late function. Recombination with RAV-1 restored the early but not the late functions, suggesting that leukosis viruses possess a gene coding for some initial event in fibroblast transformation but lack the gene(s) required for full expression (maintenance) of the transformed state. Moreover, as shown by the replicative properties of the mutant, the early gene of transformation initiation is apparently not involved in virus replication.

- 5616 G-BAND ANALYSIS IN A SERIALY TRANSPLANTED ROUS RAT SARCOMA. (Eng.) Levan, G. (Inst. Genetics, S-22362 Lund, Sweden); Mitelman, F. *Hereditas* 80(1):140-145; 1975.

The current chromosomal status of a Rous virus-induced sarcoma carried for over 300 passages *in vivo* was compared with that observed on earlier occasions. The stemline number in different regions of the primary tumor was 38, 42, and 45 chromosomes. The latter karyotype dominated completely at the next chromosomal study; it consisted of a normal male chromosome set with one C12 and two B group chromosomes in excess. Later one chromosome A2 and one B group chromosome fused in their centromeric regions to form a large m marker. This karyotype dominated up to passage 127. In passages 140-147, the stemline num-

ber dropped to 43 and the stemline karyotype was variable with one to three markers. At the 308th passage, the stemline still had 43 chromosomes, 34 of which were normal rat chromosomes, but nine were markers. As determined by G-band analysis, the sarcoma contained 13 unchanged pairs, five monosomies, and one trisomy (B7). Only two normal chromosomes were completely lost. The trisomy observed for B7 is in accordance with other studies suggesting that the addition of a B group chromosome is predetermined in Rous virus-induced sarcomas. The data show that the stemline karyotype of the tumor can remain fairly constant for many generations but that the stemline population can be radically altered on specific occasions.

5617 PREFERENTIAL INHIBITION OF GROWTH AND PROTEIN SYNTHESIS IN ROUS SARCOMA VIRUS TRANSFORMED CELLS BY DIPHTHERIA TOXIN. (Eng.) Iglewski, B. H. (Univ. Oregon Med. Sch., Portland); Rittenberg, M. B.; Iglewski, W. J. *Virology* 65 (1):272-275; 1975.

To determine whether altered sensitivity to diphtheria toxin accompanies viral-induced transformations, protein synthesis was studied in Schmidt-Ruppin Rous sarcoma virus-transformed (subgroup A, SR-RSV-A) embryo cells and virus-induced tumors. Sarcomas were induced by injection of 10^6 focus forming units into 1- to 3-day-old chicks and harvested ten days later. SR-RSV-A transformed cells were approximately ten times more sensitive to diphtheria toxin than normal cells. Protein synthesis in SR-RSV-A cells was inhibited 90% by 0.3 μ g toxin, while normal cells required 3.0 μ g toxin for 83% inhibition. Sarcomas induced *in vivo* were much more sensitive to the toxin than cells from breast, muscle, or bone marrow removed from the same animal. These results demonstrate that increased sensitivity to diphtheria toxin correlate with *in vitro* transformation by Rous sarcoma virus and with the increased sensitivity of RSV tumors induced *in vivo*. Thus, SR-RSV-A transformed and normal fibroblasts provide a good model for studying the mechanisms of differential sensitivity to diphtheria toxin in matched cell types.

5618 STUDIES ON THE OUTER SURFACE OF NORMAL AND RSV-TRANSFORMED BHK FIBROBLAST PLASMA MEMBRANE. (Eng.) Comoglio, P. M. (Univ. Torino, Sch. Medicine, 10126 Torino, Italy); Tarone, G.; Prat, M.; Bertini, M. *Exp. Cell. Res.* 93(2):402-410; 1975.

To study the cell surface structure of normal and Rous sarcoma virus (RSV)-transformed hamster BHK fibroblasts, trinitrobenzene sulfonate (TNBS) was used to selectively label the cell surfaces. The extra trinitrophenyl (TNP) groups bound on the cell surface after selective surface labeling were purified by cell fractionation followed by affinity chromatography using purified rabbit anti-DNA antibodies covalently linked to Sepharose 4B. The purified TNP proteins were then analyzed by sodium dodecyl sulfate (SDS) acrylamide gel electrophoresis,

and the number of TNP groups linked to the cells was determined by measuring the light absorption at 348 nm. Quantitation of the TNP bound to the cellular lipid fraction was also achieved by measuring the light absorption at 337 nm. TNP-labeling bound a sufficient number of TNP groups for visualization by direct immunofluorescence. Two cell shapes were noted at subconfluent density: fusiform cells with spread cytoplasm, and round cells. The fluorescence pattern and intensity were virtually the same for both forms in normal and transformed fibroblasts. Trypsin removed 70-80% of the TNP groups bound to the cell surface. Most of the remaining TNP groups were recovered in the plasma membrane fractions of the cells, a small percentage (less than 4%) being found in the mitochondria. The normal cells bound 3.3×10^{-12} mM TNP/cell, whereas the transformed cells bound about 14.2×10^{-12} mM/cell; this difference was highly significant. No significant difference was detected in the amount of TNP linked to the lipid fraction from normal and transformed BHK cells. The reaction kinetics curves for TNBS and its binding groups showed greater velocity in the case of the transformed cells, although there was no appreciable difference in the velocity constant. The SDS acrylamide patterns of the TNP-labeled membrane proteins purified from the normal and the transformed cells showed only minor differences. It is concluded that the increased exposure to TNBS-binding groups in the transformed cells was due mainly to different binding properties of the membrane proteins toward the probe, rather than to the appearance of new surface components on the transformed cells.

5619 SENSITIVITY OF NORMAL AND ROUS VIRUS-TRANSFORMED LINES OF ARMENIAN HAMSTER CELLS TO INFECTIOUS VIRUSES. (Rus.) Nadzharyan, N. U. (Inst. Roentgenol. Oncol., Min. Publ. Health Armenian SSR, Erevan, U.S.S.R.); Kamalyan, L. A. *Vopr. Virusol.* (2):167-171; 1975.

The capacity of a normal Armenian hamster embryonal cell line (NKhET), of a Rous virus-transformed, virus-transformed, virus-producing cell line (SKhET Sh-R), and of another Rous-virus-transformed cell line not producing virus (SKhET K-3) to support vaccinia and Newcastle disease virus replication was studied. Both normal and transformed cells were able to support the reproduction of vaccinia and Newcastle disease virus, while the replication of vaccinia virus was associated with a considerable cytopathogenic effect depending on the virus count. The replication of Newcastle disease virus was not associated with any cytopathogenic effect. There was no difference in the rate of replication of vaccinia virus in normal and transformed cell cultures, except for a depression of its replication in SKhET Sh-R cell line, which was due to the interference between active Rous virus and vaccinia virus in these cell cultures, since the SKhET Sh-R cells were found to produce negligible quantity of interferon (2-4 U/ml). The infectious viruses caused no activation of Rous virus genome in the virogenic SKhET K-3 cell line.

- 5620 CYTOPATHOGENICITY OF CYTOMEGALOVIRUS TO HUMAN ECTO- AND ENDOCERVICAL EPITHELIAL CELLS *IN VITRO*. (Eng.) Vesterinen, E. (I Dept. Obstetrics Gynecology, Univ. Central Hosp., Helsinki, Finland); Leinikki, P.; Saksela, E. *Acta Cytol. (Baltimore)* 19(5):473-481; 1975.

Cellular alterations induced by cytomegalovirus in epithelial cells from human ecto- and endocervix, as well as the production of the infectious virus and viral antigens were investigated. Ecto- and endocervical cultures were initiated from patients hysterectomized for uterine leiomyomas. Both types of cultures were infected with cytomegalovirus. The cultures were submitted for histological and indirect immunofluorescence studies. The cells were caused to react with purified gamma globulin from a convalescent patient and were stained with anti-human fluorescein isothiocyanate-conjugated sheep gamma globulin. Virus isolations were performed by inoculating supernatant fluids into a continuous human fibroblast cell line. The ectocervical cells grew in mosaic-like regular epithelial patterns, whereas endocervical cultures had a poorer intercellular cohesion, irregular polygonal cell form, and curved cytoplasmic processes. Ectocervical cells were resistant to cytomegalovirus infection. In contrast, endocervical cultures supported the growth of cytomegalovirus, and 30% of the explanted colonies showed cytologic alterations as well as virus-specific immunofluorescence. It is concluded that the endocervical epithelial cells may be the site of the replication of human cytomegalovirus.

- 5621 ABSENCE OF INFECTIOUS EPSTEIN-BARR VIRUS IN BLOOD IN ACUTE INFECTIOUS MONONUCLEOSIS. (Eng.) Rickinson, A. B. (Univ. Bristol, Medical Sch., University Walk, Bristol BS8 1TD, U.K.); Epstein, M. A.; Crawford, D. H. *Nature* 258(5532): 236-238; 1975.

To determine whether infectious mononucleosis (IM) patients with clinically manifest disease have infectious Epstein-Barr (EB) virus in the circulation, heparinized blood samples were taken from seven patients with acute heterophile antibody-positive IM at 1-4 wk after onset of symptoms. Cultures of mononuclear cells from centrifuged blood samples were observed for eight weeks for evidence of transformation; in addition, the plasma and two mononuclear cell extracts from each patient were assessed for their ability to transform cultures of fetal WBC over a period of eight weeks. The plasma and extracts were pretreated with either antiserum to EB virus or with EB virus-negative serum. No transformation occurred in fetal cell cultures exposed to IM plasma or in extracts of fresh mononuclear cells. In contrast, 5 of 7 cell extracts prepared after three days of culture showed detectable WBC-transforming ability. This ability was manifest only with the extracts pretreated with negative serum and was abolished by pretreatment with neutralizing antiserum. After three days of culture, extracts that produced infectious EB in culture were those with the highest incidence of transformation when cultured alone. All seven patients had detect-

able neutralizing antibodies to EB virus; seven had antibodies to antiviral capsid antigen; and two had low antinuclear antigen titers. These results show that infectious EB virus is not present in the blood in acute IM. The data support the idea that infectious virus originates from a small number of peripheral IM lymphocytes that carry the EB viral genome in a noninfectious form *in vivo*, but are activated to a cycle of virus production *in vitro*.

- 5622 ON EBNA. (Jpn.) Suzuki, M. (Kumamoto Univ. Medical Sch., Kumamoto, Japan). *Virus (Tokyo)* 24(1):126-127; 1974.

EBNA, a specific Epstein-Barr virus (EBV) antigen, was detected in human cells by the fluorescent antibody complement method and the transformation activities of this virus were investigated. Cells proven by other methods to have the EBV genome, cells not proven to have EBV genome, and human umbilical cord blood cells were exposed to a mixture of EBNA antibody-positive human blood and EBV antibody-negative blood (the human complement), and then to the anti-human complement fluorescent antibody. A culture of WBC from human umbilical cord blood incubated with EBV was also prepared. EBNA was detected in almost all of the EBV genome possessing cells by the fluorescent antibody method using the human complement line but not with a guinea pig complement line. EBNA was not detected in cells without EBV genome or human umbilical cord WBC. In human umbilical cord WBC that had been inoculated with EBV, EBNA-possessing cells were detected followed by the detection of VCA-possessing cells. The author suggests that EBNA-positive cells are transformed cells.

- 5623 EPSTEIN-BARR VIRUS ANTIBODIES IN PATIENTS WITH CARCINOMA OF THE NASOPHARYNX AND CARCINOMA OF OTHER SITES IN THE HEAD AND NECK. (Eng.) Sako, K. (Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14263); Minowada, J.; Marchetta, F. C. *Am. J. Surg.* 130(4):437-439; 1975.

Epstein-Barr virus (EBV) antibodies in patients with carcinoma of the nasopharynx were assayed as indicators of the possible involvement of the virus in carcinoma of the nasopharynx. Serum was collected from 23 patients with nasopharyngeal carcinoma, twelve of whom had active disease and eleven of whom had previously been treated with radiation therapy and had no clinical evidence of active disease. Serum was also obtained from 86 patients with carcinoma of other sites in the head and neck and from 222 age-matched controls. A Burkitt lymphoma cell line persistently infected with EBV was used as antigen. The antigen cell smear was stained with 2-fold dilutions of the serum ranging from 1:2 to 1:5.2 and then stained with fluorescein isothiocyanate-conjugated goat antihuman IgG. The mean anti-EBV titer in the 222 controls was 1:1188. The 86 patients with cancer at other sites of the head and neck had a mean anti-EBV titer of 1:1400. The 23 patients with nasopharyngeal cancer had a mean anti-EBV titer of 1:2671 which was significantly higher ($p < 0.01$ by *t* test) than the mean

titers of either of the other two groups. 63% of the patients without active disease and 83% of the patients with active disease had elevated antibody titers. These findings support the suggestion of an association between the Epstein-Barr virus and nasopharyngeal carcinoma.

- 5624 EVIDENCE FOR A NON-HEMIN REGULATED TRANSLATIONAL REPRESSOR IN FRIEND LEUKEMIA VIRUS TRANSFORMED MURINE PROERYTHROBLASTS. (Eng.) Gimadevilla, J. M. (Clayton Foundation Biochemical Inst., Univ. Texas, Austin, Tex. 78712); Hardesty, B. *Biochem. Biophys. Res. Comm.* 63(4):931-937; 1975.

Lysates prepared from Friend leukemia-virus-transformed murine proerythroblasts were not significantly stimulated by hemin over a wide concentration range. Protein synthesis was the measure of stimulation by hemin. Mixing of rabbit reticulocyte and Friend leukemia cell lysates, in the absence or presence of added hemin, resulted in the inhibition of synthesis of reticulocyte proteins. The initial rate in the mixed lysate system is approximately equal to the sum of rates of the lysates, with or without added hemin. This result suggests that the inhibition may be at peptide initiation. A translational repressor has been partially purified from these leukemic spleen cells.

- 5625 EFFECT OF PROTEASE INHIBITORS ON FOCUS FORMATION BY MURINE SARCOMA VIRUS. (Eng.) Yuasa, Y. (Inst. of Medical Science, Univ. of Tokyo, Takanawa, Tokyo 108, Japan); Shimojo, H.; Aoyagi, T.; Umezawa, H. *J. Natl. Cancer Inst.* 54(5):1255-1256; 1975.

Six protease inhibitors, isolated from various species of actinomycetes, were tested for their effect on focus formation by murine sarcoma virus (MuSV). The isolated and purified protease inhibitors tested included: leupeptin, antipain, chymostatin, elastatinal, pepstatin, and phosphoramidon. YH-7 mouse cells, established from the lung tissue of C57BL/6 mouse embryos, were seeded in cultures; the Moloney strain of MSV (M-MuSV) was added after four days incubation at 36 C. Each protease inhibitor was added immediately after virus absorption, and M-MuSV foci were counted after four days. Pepstatin effected an 80% reduction in the foci, while the other inhibitors were without effect. The inhibitory effect of pepstatin was correlated with its concentration. Pepstatin was found to inhibit virus yield, but did not significantly lower the plating efficiency of YH-7 cells. Focus formation was distinctly inhibited when the cells were exposed to pepstatin before virus adsorption, and in the late stage of incubation. However, inhibition was not distinct when pepstatin was removed in the early stages of incubation. The observation of a two-hit dose-response curve indicates that pepstatin inhibits initial and subsequent infection with M-MuSV at an early stage, i.e., adsorption, penetration, or uncoating. In addition, pepstatin appears to retard infection with M-MuSV and, consequently, focus formation.

- 5626 ABERRANT VIRUSES IN CELLS INFECTED WITH MURINE SARCOMA VIRUS-FELINE LEUKEMIA VIRUS. (Eng.) Al-Adhami, R. (Univ. Kansas Med. Cent., Kansas City); Chapman, A. L. *J. Natl. Cancer Inst.* 54(3):763-766; 1975.

An unusual type of virus that was observed when a feline leukemia virus (FeLV) pseudotype of murine sarcoma virus (MuSV), obtained by cocentrifugation procedures, infected feline embryo cells (FEF) and two Crandell cat cell lines (CrFK1, CrFK2) is described. Before infection, all cells were pretreated with DEAE-dextran (40 µg/ml, 20 min, 37 C) to enhance virus uptake. The cells were examined with the electron microscope. When all three cell cultures were infected with MuSV-FeLV (3.6×10^4 focus forming units/ 1×10^6 cells), only FEF and CrFK2 were transformed, and only these showed normal and aberrant virus. The CrFK1 infected with MuSV-FeLV did not transform but did replicate normal type-C virus with a 50-A intermediate coat. The virus replicated in the two transformed lines showed three particles: a normal particle with a 50-A intermediate coat, a normal particle with a 100-A intermediate coat, and an aberrant particle with a 100-A intermediate coat. The results suggest that morphologically aberrant particles correlate with cell transformation, and that the transformed cell infected with MuSV-FeLV replicates three morphologically different viruses.

- 5627 MECHANISM OF GIANT CELL FORMATION IN RFL-CELLS WITH INFECTION OF MURINE LEUKEMIA VIRUS. (Jpn.) Koga, M. (Faculty Medicine, Kyushu Univ., Fukuoka, Japan). *Fukuoka Acta Med.* 66(2):92-98; 1975.

RFL cells, originating from Wistar-King A strain rat lung, were shown to produce multinucleated giant cells following infection with Gross or Moloney murine leukemia viruses (MuLV). Using cinematography and autoradiography, the giant cell formation was observed to occur by cell fusion rather than by nuclear division without cytoplasmic cleavage. Giant cell formation was not induced by adding UV-irradiated MuLV and was prevented by cytosine arabinoside if the compound was added within eight hours post-infection. Virus was not detectable in the supernatant medium of the infected cells but was found at a very low level in extracts of the cells. It was concluded that the fusion of RFL cells represented the activity of a part of the viral genome.

- 5628 INFECTION OF PREIMPLANTATION MOUSE EMBRYOS AND OF NEWBORN MICE WITH LEUKEMIA VIRUS: TISSUE DISTRIBUTION OF VIRAL DNA AND RNA AND LEUKEMOGENESIS IN THE ADULT ANIMAL. (Eng.) Jaenisch, R. (Salk Inst. for Biological Studies, Post Office Box 1809, San Diego, Calif. 92112); Fan, H.; Croker, B. *Proc. Natl. Acad. Sci. USA* 72(10):4008-4012; 1975.

Explanted BALB/c mouse embryos derived from low leukemia incidence strains were infected with Mo-

loney murine leukemia virus (M-MuLV) at the 4-8 cell stage of development. After cultivation *in vitro* to the blastocyst stage, the embryos were surgically transferred to the uteri of pseudo-pregnant surrogate mothers. Of 15 animals born, one developed a leukemia at eight weeks of age. When the mouse was autopsied, this leukemia was found to be of the lymphatic type, as is typical for the M-MuLV-induced disease. In addition, infectious M-MuLV virus was isolated from the serum. Molecular hybridization tests for the presence of M-MuLV-specific sequences were conducted on DNA and RNA extracted from thymus, testes, lung, kidney, lymph node, spleen, liver, and brain of the M-MuLV-infected mouse and from the kidney and liver of control mice. The DNA-DNA reannealing experiments revealed the presence of two classes of M-MuLV-specific sequences in equal concentrations in all tissues tested. The less abundant class of M-MuLV-specific sequences was not detected in control tissues or in nontarget tissues of leukemic animals infected at birth. The results are consistent with the working hypothesis that the virus is integrated in all cells of the animal, possibly including the germ line. Fifty to 100 times more M-MuLV-specific RNA was detected in tumor tissues than was found in nontarget organs such as liver, brain, and testes. Since all organs contained the same amount of virus-specific DNA, these results indicate that the M-MuLV-specific DNA can be differentially expressed in different tissues.

5629 MURINE SARCOMA VIRUS PSEUDOTYPES ACQUIRE A DETERMINANT SPECIFYING N OR B TROPISM FROM LEUKAEMIA VIRUS DURING RESCUE. (Eng.) Bassin, R. H. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Duran-Troise, G.; Gerwin, B. I.; Gisselbrecht, S.; Rein, A. *Nature* 256(5514):223-225; 1975.

Several isolates of defective murine sarcoma virus (MSV) were tested to detect the acquisition of N- and B-tropism (the ability to induce XC plaque formation after infection of mouse N- or B-type cells, which differ at a single genetic locus Fv-1) from murine leukemia virus (MuLV). Three MSV-Moloney stocks were rescued from MSV-transformed BALB/3T3 nonproducer cells with either N-, B-, or NB-tropic MuLV. MSV was collected 11 days after superinfection and assayed on B-type (BALB/3T3) cells, N-type cells (C3H), and on dually permissive cells (3T3FL). MSV stocks rescued with either N- or B-tropic MuLV formed foci equally efficient in dually permissive cells when assayed in the presence of NB-tropic helper virus MuLV. MSV rescued with dually tropic MuLV was equally efficient in all three cell types. MSV rescued with N-tropic MuLV was almost 200 times as efficient at focus formation on N-type cells as on B-type cells, whereas the same MSV rescued with B-tropic helper virus MuLV was only 1/20 as efficient on N-type cells. Because the assay was conducted with added MuLV NB-tropic helper virus, the possibility of interaction between MSV and MuLV added for the assay was investigated. A longer assay procedure was performed with no added helper virus. Plates were counted at 5 days and at 11 to 13 days. MSV rescued with N-, B- or NB-tropic MuLV exhibited the

same tropism as the helper virus used for rescue. Restriction of N-tropism by B cells was more pronounced than that of B-tropic helper virus by N-type cells. Similar experiments using dually permissive S+L-3T3 FL cells as the source of MSV yielded similar results, demonstrating that the Fv-1 restriction exhibited by cells from which MSV is rescued is not a major factor in determining MSV tropism. Further experiments were performed using BALB/S+L cells, K-BALB cells, and a line of Harvey sarcoma virus-transformed 3T3 FL cells with similar results. The authors conclude that the infection of MSV is subject to Fv-1 restriction. The tropism of the defective MSV particle is determined by its helper MuLV during rescue. N- or B-tropism is a phenotypic helper-dependent characteristic of MSV pseudotypes.

5630 VIRUS-SPECIFIC PRECURSOR POLYPEPTIDES IN CELLS INFECTED WITH RAUSCHER LEUKEMIA VIRUS. (Eng.) van Zaane, D. (Dept. Biochemistry, Univ. Nijmegen, Geert Grooteplein Noord 21, Nijmegen, The Netherlands); Gielkens, A. L. J.; Dekker-Michielsen, M. J. A.; Bloemers, H. P. J. *Virology* 67(2):544-552; 1975.

Virus-specific protein synthesis in JLS-V9 cells infected with Rauscher leukemia virus (R-MuLV) was studied by an immunoprecipitation technique. One low molecular weight virion protein (p15) could be detected intracellularly following a decrease in the amount of two nonvirion polypeptides with molecular weights of 82,000 and 65,000. These high molecular weight polypeptides were converted into the virion proteins p30, p15, and p12b, as shown by incubation of the cell lysate. The results suggest that the conversion took place on membrane structures; it was not inhibited by three different protease inhibitors. However, growth of cells in the presence of the arginine analog canavanine (3.3 mM) prevented formation of the 65,000-dalton polypeptide and the p15 virion polypeptide. It is concluded that the 82,000- and 65,000-dalton polypeptides are precursors of virion proteins.

5631 MITOSIS IS REQUIRED FOR PRODUCTION OF MURINE LEUKEMIA VIRUS AND STRUCTURAL PROTEINS DURING *DE NOVO* INFECTION. (Eng.) Fischinger, P. J. (National Cancer Inst., Bethesda, Md. 20014); Tuttle-Fuller, N.; Huper, G.; Bolognesi, D. P. *J. Virol.* 16(2):267-274; 1975.

Cloned 3T3FL cells were synchronized in G1 phase of the cell cycle by deprivation of multiplication stimulatory activity of serum and were then infected with Moloney leukemia virus in order to examine the cycle of infection. Eclipse period of virus could be made to vary from less than 10 to 34 hr. All virus release was completely dependent and occurred immediately after the first mitosis following serum reconstitution. Virus yield was not affected by the time of virus inoculation as related to the cell DNA synthetic phase. Colchicine (4 µg) arrested the cells in mitosis and prevented the formation of infectious virus. Viral proteins p10, p30, and gp71 were

assayed in cell lysates during the growth curve of virus in synchronized cells. The group-specific determinants of each protein were measured in a competition radioimmunoassay. None of the virus proteins appeared during the eclipse period of the virus. All three proteins appeared simultaneously, coincident with mitosis, and continued to rise during the G1 phase. The absolute quantities of each protein were proportional to the amount of Moloney leukemia virus produced. The relative amounts of some of the viral proteins in the cell did not correspond to their content in purified virions, suggesting several possible mechanisms of control; these include (a) to select turnover of some viral proteins; (b) redundant information within the viral message; (c) transcriptional or translational polarity; and (d) derivation of some viral structural protein from endogenous oncornavirus.

5632 ACUTE OCULAR INFECTION BY TYPE 2 HERPES SIMPLEX VIRUS IN ADULTS: REPORT OF TWO CASES. (Eng.) Oh, J. O. (Francis, I. Proctor Foundation, Univ. California, San Francisco, Calif. 94143); Kimura, S. J.; Ostler, H. B. *Arch. Ophthalmol.* 93(11):1127-1129; 1975.

Two cases of ocular infection by type 2 herpes simplex virus (HSV) in adults (a 38-yr-old man and a 58-yr-old woman) are reported. The man had an acute blepharconjunctivitis, and the woman had an acute keratoconjunctivitis. Genital infections had preceded the eye infections, and type 2 HSV was isolated from the eyes of both patients and from the genital lesions of the man. This strongly suggests transmission of type 2 HSV from the genital site to the eye.

5633 GENETIC ASPECTS OF SUSCEPTIBILITY TO LEUKEMIA IN MICE. (Eng.) Hilgers, J. (Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam-1004, Netherlands); Lamie, F. *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 254-259.

Genetic aspects of leukemia susceptibility were studied in the AKR/FuRd mouse strain, which shows a high incidence of spontaneous lymphatic leukemia, and in several strains with a low incidence of spontaneous lymphatic leukemia. Quantitative immunofluorescence absorption on acetone-fixed cells (IFA) was used to detect the group-specific antigen of naturally occurring murine leukemia virus (MuLV-s) in the spleens of these mice, and the IFC test was used to detect infectious MuLV on secondary embryo cultures to determine N- and B-tropism *in vitro*. There was a good correlation between repression of MuLV-gs levels and the B-tropism of the low incidence strains, indicating a pronounced, dominant effect of the Fv-1 locus. The N-tropic group IID strains of European origin did not carry genes for repression of the antigen in F1 hybrids, while a slight but definite repression was observed

with N-tropic strains of American origin, notably the C3Hf strain. With regard to the effect of the H-2 locus on the MuLV-gs levels in F1 hybrids, the H-2^b allele clearly had a less dramatic repressive effect compared with the Fv-1^b influence. The results of IFA tests for MuLV-gs in the spleens of segregating populations between AKR/FuRd and GR and St demonstrated that 97.5% of all backcrosses were positive. The transmission of the antigen was chromosomal. The results indicate that at least five induction genes are involved in the expression of MuLV-gs. It is not clear whether one or more of these genes is responsible for the high incidence of spontaneous leukemia in AKR mice.

5634 STRAIN-DEPENDENT EXPRESSION OF ENDOGENOUS MOUSE-TROPIC LEUKEMIA VIRUSES IN CHEMICALLY INDUCED MURINE LEUKEMIAS. (Eng.) Odaka, T. (Inst. Medical Science, P.O. Takanawa, Tokyo 108, Japan). *Int. J. Cancer* 16(4):622-628; 1975.

The effects of two chemical carcinogens, nitrosobutylurea (NBU) and 7,12-dimethylbenz(a)anthracene (DMBA), on the expression of endogenous N- and B-tropic viruses were studied. The mice used were from two inbred strains, C57BL/6 and DDD-FV, and from 13 partially inbred strains derived from the cross of C57BL/6 with DDD-FV. These mouse strains are classified into three groups by the pattern of expression of endogenous viruses in normal, aged mice: (a) negative for both viruses; (b) positive for N-tropic virus only; and (c) positive for both viruses. NBU (0.04%) was given in drinking water for two months to 5-wk-old mice. One- to four-day old mice were given sc injections of 1/10 ml of 1 mg/ml solution of DMBA. All treated mice were tested at various intervals by the UV-XC procedure for the viruses in the spleens and other enlarged organs. Mice whose cells or cell extracts, irrespective of tissue origin, produced XC plaques on first culture or subculture of Fv-1ⁿⁿ and/or FV-1^{bb} cells were scored as virus-positive. If the specimens from all the tested organs of a mouse produced no plaques on cells of both types after subculture, the mouse was considered negative for virus. Irrespective of the presence or absence of leukemias, the carcinogen-treated mice showed the same pattern of expression of endogenous viruses as that of non-treated normal mice. It is concluded that the activation of the endogenous viruses is dependent on the mouse strains and that the growth of the activated viruses is not a necessary step for the chemical induction of leukemias.

5635 A p60 POLYPEPTIDE IN THE FELINE LEUKEMIA VIRUS PSEUDOTYPE OF MOLONEY SARCOMA VIRUS WITH MURINE LEUKEMIA VIRUS p30 ANTIGENIC DETERMINANTS. (Eng.) Oskarsson, M. K. (Natl. Cancer Inst., Bethesda, Md. 20014); Robey, W. G.; Harris, C. L.; Fischinger, P. J.; Haapala, D. K.; Vande Woude, G. F. *Proc. Natl. Acad. Sci. USA* 72(6):2380-2384; 1975.

A 60,000-dalton polypeptide (p60) was identified in the feline leukemia virus (FeLV) pseudotype of

Moloney sarcoma virus [MSV(FeLV)]. The MSV(FeLV) complex was analyzed by polyacrylamide gel electrophoresis, and the p60 polypeptide was purified from the complex by guanidine agarose chromatography. The antigenicity of p60 was determined by gel immunodiffusion against several antisera specific for murine and feline viral antigens, and p60 and the murine p30 polypeptide were compared by peptide fingerprinting. In addition, p60 was incubated for 30 min at 37 C with 0.2% wt/wt trypsin and chymotrypsin, and the products were analyzed by polyacrylamide gel electrophoresis. The immunological properties of the products were also studied by guanidine agarose chromatography, polyacrylamide gel electrophoresis, and Ouchterlony analysis. The p60 polypeptide was the major component of the MSV(FeLV) complex, being present in higher concentrations than either p30 or the feline p27 polypeptide. p60 was not detected in the FeLV helper, in the murine leukemia virus (MuLV) pseudotype of MSV [MSV(MuLV)], or in MuLV. Purified p60 cross-reacted immunologically with murine p30 group antiserum and contained several interspecies determinants (MuLV gs-1); the group specific determinant of FeLV p27 was not detected. Comparison of the peptide fingerprints of p60 and p30 showed at least 25 peptides in common and at least ten unrelated peptides. Limited digestion of p60 with either trypsin or chymotrypsin produced p30-p35 and p20 peptides that retained the MuLV p30 group and interspecies antigenic activities. The p30 produced by both enzymes comigrated in polyacrylamide gels with the murine p30 of MSV(FeLV), indicating that p60 may be an uncleaved precursor to p30.

- 5636 ANATOMY OF HERPES SIMPLEX DNA. II. SIZE, COMPOSITION, AND ARRANGEMENT OF INVERTED TERMINAL REPETITIONS. (Eng.) Wadsworth, S. (Dept. Microbiol., Univ. Chicago, Ill.); Jacob, R. J.; Roizman, B. *J. Virol.* 15(6):1487-1497; 1975.

Electron microscopic studies were conducted on denatured and partially denatured herpes simplex virus type 1 DNA as a part of a larger investigation aimed at mapping the functions expressed by the virus. Herpes simplex virus 1 (F1) DNA was prepared from cells infected at a multiplicity of 5 plaque formation units (PFU)/cell. Herpes simplex virus 1 (Justin) DNA was prepared from cells infected at a multiplicity of 0.01 PFU/cell. In both instances, the cells were labeled with [³H]thymidine. DNA was extracted from virions purified from cytoplasmic extracts or from purified nucleocapsids. Viral DNA was denatured with either formamide or alkali. Approximately 10-15% of total DNA was recovered as intact strands. The intact strands, or lambda exonuclease-digested DNA, at concentrations of 1 µg/ml or less, were annealed in 66% (vol/vol) formamide. Two procedures were used to prepare DNA-cytochrome c film: (1) the aqueous method of spreading DNA in a cytochrome c film was used for partially denatured DNA molecules; and (2) the formamide method of spreading DNA in a cytochrome c film was used for the visualization of the self-annealed intact DNA strands. Electron microscopy showed herpes simplex virus 1 DNA consisting of two unequal regions, each bounded by inverted redundant

sequences. The region L (70% of the contour length of the DNA) separated the left terminal region a_1b from its inverted repeat $b'a_1$, each of which comprised 6% of the DNA. The region S (9.4% of the DNA) separated the right terminal region ca_s (4.3% of the DNA) from its inverted repeat $a_s'c'$. The regions of the two termini that are inverted and repeated internal differed in topology. Thus, ca_s is guanine- plus cytosine-rich, whereas only the terminal 1% of the a_1b region (designated as subregion a_1) is guanine- plus cytosine-rich. The anatomy of herpes simplex virus 1 DNA appears to be different from that of an DNA virus of eukaryotic cells previously reported.

- 5637 GENETICS OF NATURAL RESISTANCE TO HERPES-VIRUS INFECTIONS IN MICE. (Eng.) Lopez, C. (Sloan-Kettering Inst., Lab. of Slow-Virus Infections, 410 East 68th St., New York, N.Y. 10021) *Nature* 258(5531):152-153; 1975.

A study of the resistance of 11 inbred mouse strains to fatal herpes simplex virus-1 infection (strain 2931, 1-10⁶ plaque-forming U [PFU]/inoculum, ip) demonstrated that the strains fell into three categories: resistant, moderately susceptible, and very susceptible. Most resistant mice survived 10⁶ PFU of HSV-1, while the LD₅₀s for moderately susceptible mice ranged from 200-1000 PFU/inoculum. For very susceptible mice, the LD₅₀s were in the range 10-70 PFU/mouse. Experiments carried out with six other HSV-1 strains showed that all but one (HEFM) had the same relative virulence in C57BL/6, BALB/c, and AJ mice as observed with strain 2931. The latter appeared more virulent than the other strains. To determine whether resistance is dominant, crosses were produced between resistant and very susceptible mice (C57BL/6 x A)F₁ and between resistant and moderately susceptible mice (C57BL/6 x BALB/c)F₁. Ninety percent of 20 (C57BL/6 x A)F₁ mice and 100% of 20 (C57BL/6 x BALB/c)F₁ mice survived inoculation with 10⁶ PFU of HSV-1, indicating that resistance was dominant. Studies of the resistance of progeny of (C57BL/6 x A)F₁ backcrossed to AJ mice and of the progeny of (C57BL/6 x BALB/c)F₁ mice backcrossed to BALB/c mice indicated that at least two and perhaps four or more genes are involved in resistance. Resistance to HSV-1 was not associated with a particular histocompatibility (H-2) allele since resistant mouse strains were of H-2^b and H-2^d types. Preliminary lymphocyte transformation studies with splenic lymphocytes from HSV-1 pretreated mice suggest that resistance may be mediated immunologically.

- 5638 SUBTYPING OF HERPES SIMPLEX VIRUS. (Eng.) Vahne, A. (Inst. of Medical Microbiology Univ. of Guldhedsgatan 10, 41346 Goteborg, Sweden); Blomberg, J.; Olofsson, S.; Lycke, E. *Acta Pathol. Microbiol. Scand.* [B] 83(5):506-512; 1975.

Various methods that may discriminate between the two subtypes of herpes simplex virus (HSV) were compared with respect to their reliability and usefulness as screening procedures. Various strains of HSV type 1 and type 2 were inoculated onto the chorioallantoic membranes (CAM) of embryonated eggs

and on green monkey kidney (GMK) cells. The strains were then classified serologically by determination of K-values and were inoculated ic into Swiss mice to determine their pathogenicity. The inhibitory effect of thymidine (0.5-2.0 mM) on the multiplication of the viruses in GMK cultures and the heat-stability of the virus-induced thymidine kinases were also investigated, as were the rates of inactivation of the viruses in the presence of AgNO₃ (40 µM) and the induction of liver necrosis in ip-inoculated Swiss mice. The results suggested that the liver necrosis test is simple as well as accurate and useful as a screening procedure. Serological typing also yielded reliable results, but this method is laborious and not applicable as a screening procedure. Determination of the heat-stability of the viral thymidine kinases must also be considered valuable as a means by which the typing of selected strains can be confirmed. The AgNO₃ test, on the other hand, did not give reproducible results and was of limited value with strains of intermediate sensitivity.

- 5639 *IN VIVO* CHARACTERISTICS OF TEMPERATURE-SENSITIVE HOST RANGE MUTANTS OF HERPES SIMPLEX VIRUS TYPE 2. (Eng.) Koment, R. W. (Univ. Miami Sch. Medicine, P.O. Box 875, Biscayne Annex, Miami, FL 33152); Rapp, F. *Intervirology* 5(1/2): 10-20; 1975.

The *in vivo* properties of four host range temperature-sensitive mutants of herpes simplex virus type 2 (HSV-2) were correlated with known *in vitro* characteristics. As the virulence of HSV-2 obscured possible oncogenicity, attenuated mutants of HSV-2 were utilized so that large amounts of the virus could be inoculated directly into newborn animals. Mutants and parental virus were inoculated into newborn and weanling mice and weanling hamsters by intracranial and sc routes, and into weanling rabbits by corneal scarification. In all cases the pattern of attenuation of mutants *in vivo* correlated with their stability *in vitro* at 39°C. The most attenuated mutant (mutant 69) was also the most consistent in its inability to induce cytopathic effects *in vitro* or to replicate under nonpermissive conditions. Conversely, the most virulent mutant (mutant 41) was the least stable under nonpermissive conditions.

- 5640 DNA SYNTHESIS IN POLYOMA VIRUS INFECTION. III. MECHANISM OF INHIBITION OF VIRAL DNA REPLICATION BY CYCLOHEXIMIDE. (Eng.) Yu, K. (Cancer Res. Lab., Univ. West. Ontario, London, Canada); *J. Virol.* 15(6):1409-1417; 1975.

The mechanism of inhibition of DNA replication in polyoma virus-infected cycloheximide-treated mouse embryo cells was studied in an attempt to understand the molecular basis for coordinate control of cellular and viral DNA synthesis. Primary cultures of mouse embryo cells were subcultured at concentrations of 5×10^5 or 15×10^5 cells/dish. Secondary cultures were grown to confluence and infected with polyoma virus at input multiplicities ranging from

50-150 plaque-forming units/cell, or they were mock-infected. Infected cells were incubated for various periods of time with medium or medium containing 10 µg cycloheximide/ml, and replicating viral DNA was labeled with [³H]thymidine. Crude sodium dodecyl sulfate lysates of cells were prepared and sedimented in neutral sucrose gradients. Replicative intermediate polyoma DNA was prepared by chromatography on benzolated-naphtholated DEAE-cellulose columns. Form I polyoma DNA was separated from alkali-denaturable replicative intermediate polyoma DNA by velocity sedimentation at alkaline pH. The pool of replicating viral DNA molecules was reduced in cycloheximide-treated cells by more than 50%, an amount consistent with inhibition of [³H]thymidine incorporation into viral DNA. The rate of conversion of replicating molecules into closed-circular DNA was not affected by cycloheximide treatment. The rate of elongation of nascent viral DNA fragments into strands of unit genome length was also unaffected by cycloheximide treatment. The results suggest that viral DNA synthesis is inhibited in the absence of protein synthesis exclusively at the level of initiation of new rounds of genome replication.

- 5641 HAMSTER α -AMANITINE-RESISTANT RNA POLYMERASE II ABLE TO TRANSCRIBE POLYOMA VIRUS GENOME IN SOMATIC CELL HYBRIDS. (Eng.) Amati, P. (International Inst. Genetics and Biophysics, C.N.R., Via Marconi 10, 80125 Naples, Italy); Blasi, F.; Di Porzio, U.; Riccio, A.; Traboni, C. *Proc. Natl. Acad. Sci. USA* 72(2):753-757; 1975.

A hamster cell line resistant to α -amanitine was isolated and characterized. Cell extracts of this mutant have an α -amanitine-resistant RNA polymerase II (nucleosidetriphosphate:RNA nucleotidyltransferase) activity as shown by DEAE-cellulose column chromatography. This mutation is dominant in interspecific hybrids with 3T3 mouse cells. Parental hamster cells were nonpermissive for polyoma virus, and α -amanitine completely inhibited growth of the virus in parental 3T3 cells. In the hybrids, polyoma virus grew with equal efficiency in the presence or absence of the drug. These results indicate that the RNA polymerase of the nonpermissive hamster cell line can participate in the correct transcription of the viral genome. Control of polyoma growth in different cell lines apparently lies at a level different from the activity of the host RNA polymerase.

- 5642 DNA POLYMERASES IN POLYOMA VIRUS-INFECTED MOUSE KIDNEY CELLS. (Eng.) Wintersberger, U. (Institut für Krebsforschung der Universität Wien, A-1090 Vienna, Austria); Wintersberger, E. *J. Virol.* 16(5):1095-1100; 1975.

The process of DNA polymerase induction was studied in polyoma virus-infected mouse kidney cells. Confluent cultures were infected with 0.4 ml of a virus suspension containing about 10^9 plaque forming U/ml. In some cases, infection was carried out in the presence of 15 µg/ml of 5-fluorodeoxyuridine (an inhibitor of DNA synthesis). Twenty-four hours after infection, the cultures were subjected to cell frac-

tionation, and DNA polymerase activity was determined by measuring the incorporation of [^3H]TMP into acid-insoluble material. Sedimentation analyses were also performed using sucrose gradients. Infection of the arrested mouse kidney cells by polyoma virus resulted in the induction of the cellular 6-8S DNA polymerase activity. The levels of this enzyme increased 2 to 3-fold in the cytoplasm and 7 to 10-fold in the nuclei and nuclear extracts. Experiments using 5-fluorodeoxyuridine indicated that the accumulation of enzyme in the nucleus was linked to active DNA synthesis. The activity and cellular distribution of the small 3.4S DNA polymerase remained unchanged. The results indicate an involvement of DNA polymerase α in the synthesis of polyoma virus DNA. They also suggest that DNA polymerase α might be a nuclear enzyme that is bound and retained more strongly in nuclei synthesizing DNA.

- 5643 ULTRASTRUCTURAL ASPECTS OF BK VIRUS UPTAKE AND REPLICATION IN HUMAN FIBROBLASTS. (Eng.) Maraldi, N. M. (Inst. Microbiology, Via San Giacomo 12, 40126 Bologna, Italy); Barbanti-Brodano*, G.; Portolani, M.; La Placa, M. *J. Gen. Virol.* 27(1):71-80; 1975.

The interaction of BK virus, a human papovavirus originally isolated from the urine of a kidney-graft recipient, with human embryonic fibroblasts was studied at the ultrastructural level. After exposure of the fibroblasts to BK virus (2.9×10^8 focus-forming U/ml), virus particles adsorbed to the plasma membrane were engulfed by pinocytosis or captured by vesicles, possibly originating from the endoplasmic reticulum, within two hours after infection. Most of the virus particles were then transported into lysosomes or into the nucleus, while a small amount of virus was found free in the cytoplasm. Virus particles entered the nucleus between 2 and 12 hr after infection, were still detectable in the nucleus at 24 hr after infection, and became morphologically undiscernible at 30 hr after infection, suggesting that a nuclear uncoating mechanism was active between 24 and 30 hr after infection. Virus progeny started to appear in the nucleus of infected cells at four days after infection, but not until 7-8 days after infection did the virus escape into the cytoplasm and cell degeneration become evident. The long replicative cycle of BK virus in permissive cells may be associated with the low yield of infectious virus produced by the infected cells, possibly as a result of the higher number of defective and interfering particles present in BK virus pools.

- 5644 PRESENCE OF ANTIBODY TO A PRIMATE RNA VIRUS IN HUMAN PLASMA. (Eng.) Kim, B. S. (La Rabida-Univ. Chicago Inst., East 65th St., at Lake Michigan, Chicago, Ill. 60649). *Nature* 257(5527):614-616; 1975.

Plasma from patients with various malignancies was tested for antibody which reacts with the Mason-Pfizer monkey virus (MPMV) core protein. The survey for antibody against labeled core protein was

done on samples from 75 individuals (67 with some malignancy; eight appearing normal) selected without regard to age, sex, stage or type of malignancy or therapy. A major protein of MPMV having a molecular wt of 25,000 (p25) was purified by a combination of agarose gel filtration and DEAE-cellulose chromatography. The p25 was iodinated with ^{125}I by the chloramine T procedure. A goat anti-rabbit antiserum gave a maximum of 72% ^{125}I indirect precipitation of a mixture of [^{125}I]-p25 and a rabbit antiserum prepared against MPMV. Indirect radio-precipitation was inhibited by MPMV virus obtained from either cultures of human (NC-37) or simian (MT) cells infected with the virus. Proteins obtained from the viral density region of disrupted non-infected cells (either line) did not cause any detectable inhibition of precipitation. The p25 appeared to be a viral protein and not a membrane component of the host cell. The individual responses for 8 normal volunteers, 8 patients with lung cancer, 13 patients with breast cancer and 9 patients with other malignancies ranged from 15-25% binding of [^{125}I]-p25, without significant differences between the means of these groups. Patients with carcinoma of the colon and leukemia, however, had levels as high as 66-70% binding; some individuals showed less antibody than the normal individual with the highest level of binding. The significance levels of differences between the means were: $p < 0.005$ for patients with carcinoma of the colon and the normal group; and $p < 0.001$ for patients with leukemia and for the normal group. It is not known if the results indicate that some individuals may have been or are infected with a virus similar to or identical with MPMV, if patients with leukemia or carcinoma of the colon are simply more prone to exposure and/or infection with the agent responsible for inducing antibody against p25 of MPMV, or if the infection is relevant to the development of malignancy. More research is needed to investigate the significance of the presence of the antibody in some cancer patients.

- 5645 ROLE OF SIMIAN VIRUS 40 GENE A FUNCTION IN MAINTENANCE OF TRANSFORMATION. (Eng.) Brugge, J. S. (Baylor Coll. Med., Houston, Tex.); Butel, J. S. *J. Virol.* 15(3):619-635; 1975.

To determine whether simian virus 40 (SV40) gene A function is involved in the maintenance of transformation, normal cells were transformed with group A mutants and were examined after growth at the permissive and nonpermissive temperatures. Morphology, saturation density, colony formation (on plastic, monolayers of normal cells, and in soft agar), 2-deoxy-D-glucose uptake, and expression of SV40 tumor and surface antigens were all studied. Multiple parameters were monitored to determine whether loss of the SV40 gene A function affected all, several or none of the characteristics of the transformed state. SV40 group A mutants A7, A28, A30 and A58, the wild type 2 and the wild type Baylor reference strains were used. Normal cells consisted of human skin cells derived from a patient with Fanconi anemia, hamster embryo fibroblast cells, and BALB/3T3 mouse cells. The group A mutant-transformed cells grown under permissive temperature formed multiple cell layers and cell

with a rounded morphology; under nonpermissive conditions, the cells were fibroblastic and highly contact-inhibited, resembling the morphology of normal cells. When cells were shifted back to the permissive temperature, they returned to the original transformed morphology within two days. Wild type-transformed cells of hamster, human, and mouse showed the same morphology at both temperatures. Group A mutant-transformed cells paralleled the rapid growth and high saturation densities of wild type-transformed cells under permissive conditions. At the nonpermissive temperature, these cells showed the slower growth rates and lower final saturation densities of normal cells. A temperature-dependent variation in colony formation was observed with mutant-transformed cells. Cells from all three species formed 4- to 51-fold fewer colonies at the nonpermissive temperature than at the permissive temperature on plastic, and 4- to 18-fold less on normal cell monolayers and on soft agar. Temperature-shift studies with normal and transformed hamster cells seeded onto plastic Petri dishes indicated that the apparent reversion of A-mutant-transformed cells to a normal phenotype is a reversible event. Both hexose uptake and expression of SV40-induced antigens were temperature-dependent. It is concluded that the continual expression of the gene A function is required for maintenance of transformation.

5646 MASON-PFIZER MONKEY VIRUS: ANALYSIS AND LOCALIZATION OF VIRION PROTEINS AND GLYCOPROTEINS. (Eng.) Schochetman, G. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Kortright, K.; Schlom*, J. *J. Virol.* 16(5):1208-1219; 1975.

The proteins and glycoproteins of Mason-Pfizer monkey virus (MPMV) and their locations in the virion were studied. Six major polypeptides of molecular wt 68,000, 27,000, 20,000, 14,000, 12,000, and 10,000 were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The cell types were: cocultivated normal embryo plus monkey mammary tumor cells, rhesus foreskin cells, NC-37 human lymphoblastoid cells, human amnion AV-3 cells. Protein gp68 was the major glycoprotein and protein gp20 (molecular wt 68,000 and 20,000 respectively) was the minor glycoprotein of the virion. Protein gp68 appears to be on the outer surface of the viral envelope, as demonstrated by lactoperoxidase-catalyzed iodination of intact virions. MPMV appears to be unrelated to type B and C RNA tumor viruses.

5647 A MAP OF TEMPERATURE-SENSITIVE MUTANTS OF SIMIAN VIRUS 40. (Eng.) Lai, C. -J. The Johns Hopkins Univ. Sch. Medicine, Baltimore, Md. 21205; Nathans, D. *Virology* 66(1):70-81; 1975.

Temperature-sensitive mutants of simian virus 40 (SV40), representing each complementation class, were mapped by marker rescue with Endo R fragments of wild-type SV40-DNA. The 41 mutants mapped covered most of the genome, but there was a notable absence of mutants mapping between 0.43 and 0.85 map units. Mutants which were defective in viral

DNA synthesis (tsA mutants) all mapped in the "early" region of the genome; 12 of 13 such mutants were clustered in about one-fourth of the "early" region between 0.32 and 0.43 map units. Mutants in complementation classes defective in a late function map in the "late" region also showed clustering: 8 of 9 B mutants mapped between 0.94 and 0.06 map units; all C mutants mapped between 0.06 and 0.11 map units; and 7 of 8 BC mutants mapped between 0.11 and 0.17 map units. D mutants, which are thought to be defective in virus uncoating at high temperature, all mapped between 0.85 and 0.94 map units, i.e., in a small segment of the "late" region. Therefore, the genomic segment associated with the defect of D mutants probably codes for a virion protein. One C mutant proved to be a double mutant with one mutation in the B region and another in the C region, both mutations being required for the tsC phenotype. On the basis of the mapping data and prior complementation tests it is suggested that B, C, and BC mutations are in one cistron, complementation occurring at the protein level.

5648 GENETIC CONTROL OF ENDOGENOUS C-TYPE VIRUS PRODUCTION IN PANCREATIC ACINAR CELLS OF C57BL/He AND C57BL/6J MICE. (Eng.) Boiocchi, M. (Division of Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, 20133 Milan, Italy); Della Torre, G.; Della Porta, G. *Proc. Nat'l. Acad. Sci. USA* 72(5):1892-1894; 1975.

Pancreas fragments from dexamethasone-treated and untreated mice were examined for C-type virus particles with the electron microscope. The following inbred strains were used: C57BL/He, C57BL/6J, BALB/c, and C31tf/Dp; hybrids of C57BL with C3Hf and BALB/c mice, and a backcross generation were also studied. All mice were treated with a single ip injection of 50 µg dexamethasone/g. All treated strains produced a large number of C particles in the cytoplasmic vacuoles except for the following: untreated C57BL/6J mice, treated C3Hf and BALB/c mice, and untreated (C57BL/6J x C3Hf)F₁ mice. Normal mice of both C57BL/He and C57BL/6J strains produce C-type particles in the pancreatic acinar cells; no particles were found in the cells of C3Hf or BALB/c. The results suggest the possibility that pancreatic cells of C57BL strains have a nonfunctional regulator gene of the C-type virus structural gene, since C-type virus structural genes are included in the genome of all previously studied species of vertebrates. Because the single *in vivo* injection of dexamethasone increased viral synthesis, different inductional mechanisms between strains are indicated.

5649 EFFECT OF HYPERTONIC CONDITIONS ON PROTEIN SYNTHESIS IN CELLS PRODUCTIVELY INFECTED WITH SIMIAN VIRUS 40. (Eng.) England, J. M. (The Wistar Inst. Anatomy and Biology, Philadelphia, Pa. 19104); Howett, M. K.; Tan, K. B. *J. Virol.* 16(5):1101-1107; 1975.

Hypertonic medium selectively suppressed the synthesis of most host cell polypeptides relative to the synthesis of simian virus 40 (SV40) capsid polypep-

tides and a minority of cellular polypeptides, notably histones. African green monkey kidney (AGMK) cells were used as hosts. Under optimal hypertonic conditions, the synthesis of the major capsid polypeptide (VP1) is enhanced about seven-fold relative to host polypeptide synthesis. [^3H]lysine-labeled peaks in cell lysates which co-migrated with SV40 capsid proteins were designated as VP1, VP2, etc. A 2-3-fold enhancement of VP4 relative to host labeling was found. The maintenance of the restricted pattern of protein synthesis caused by hypertonic medium was dependent on continual peptide chain initiation. The resistance of viral protein synthesis to hypertonic conditions provides a means of detecting relatively low levels of intracellular viral protein synthesis. Analysis of the specific activity of the acid-soluble [^3H]lysine pool indicated that the rate of incorporation of [^3H]lysine into protein was an overestimation of the actual rate of overall protein synthesis occurring in cells exposed to hypertonic as compared to isotonic conditions. Since it is likely that both cellular and viral protein synthesis draw lysine from a single pool, this change in pool specific activity does not affect the analysis of relative rates of protein synthesis at a given level of tonicity. This resistance to hypertonic conditions may be a fundamental difference between peptide-chain initiation by the virus as compared to the host.

- 5650 INHIBITION OF VIRAL REVERSE TRANSCRIPTASE AND LEUKEMOGENESIS BY MODIFIED NUCLEIC ACIDS. (Ger.) Chandra, P. (Gustav-Embsden-Zentrum der biologischen Chemie Abt. f. Molekularbiologie D-6000 Frankfurt am Main 70 Theodor-Stern-Kai 7 Bundesrepublik Deutschland); Kornhuber, B.; Gericke, D.; Gotz, A.; Ebner, U. *Z. Krebsforsch.* 83(3):239-249; 1975.

The effect of mercaptopolycytidylic acid (MPC) and its analogs (chemically modified polycytidylic acid containing 5-SH cytidylic bases in the polymerase) on viral reverse transcriptase and on leukemogenesis was studied. Partially thiolated polycytidylic acids (MPC I, MPC II and MPC III containing 1.7%, 3.5%, and 8.6% 5-mercaptopolycytidylate U, respectively) inhibited the reverse transcriptase of Friend leukemia virus in the endogenic reaction as well as in the presence of poly rA · (dT)₁₄ (hybrid polymer composed of one polyadenylic acid strand and of a polydesoxythymidylic acid strand) or poly (dA-dT) (bicatenary synthetic DNA composed of alternating desoxyadenylic acid and desoxythymidylic acid molecules) templates. The inhibitory activities were directly related to the rate of thiolation. In a bacterial reverse transcriptase (*Escherichia coli*-K₁₂ with denatured calf thymus DNA as template), MPC I, MPC II and MPC III showed no inhibitory activity, which seems to indicate a specific bond of MPC with the leukemia virus reverse transcriptase. The inhibitory activity of MPC was found to be due to a complex formation with leukemia virus reverse transcriptase. Biological experiments showed about 60% inhibition of the leukemogenic potential of cell-free spleen extracts from Friend leukemia virus-infected mice by MPC III. Preliminary clinical trials with MPC alone or in com-

bination with polyinosinic acid showed good response in advanced, therapy-resistant cases of acute lymphatic leukemia in children.

- 5651 TEMPERATURE-DEPENDENT ROSETTE FORMATION BY MOUSE LYMPHOMA CELLS AS A RESULT OF VIRAL HEMADSORPTION. (Eng.) Hiai, H. (Aichi Cancer Center Res. Inst., Tashiro-cho Chikusa-ku, Nagoya 464, Japan). *J. Natl. Cancer Inst.* 55(4):961-969; 1975.

Temperature-dependent rosette formation by some mouse lymphoma cells after viral hemadsorption is characterized, and the properties of rosette-inhibiting factors in normal sera are described. Cells from several mouse lymphomas formed rosettes with nonsensitized foreign RBC through C-type virus particles clustered on the cell surface in serum-free medium held at 4 C. This type of rosetting was found most typically in a lymphoma induced by Rauscher leukemia virus in tissue culture (RD-12), but it also occurred in 23 of 61 spontaneous thymic lymphomas in AKR mice. Chemically (*N*-nitrosobutylurea) or X-ray-induced leukemias and spontaneous reticulum cell sarcomas did not form rosettes. The nature of the rosette formation may be interpreted as viral hemadsorption, with a possible relationship to hemagglutination by murine leukemia viruses. The receptor on virus particles was trypsin-sensitive and showed high affinity to serum inhibitors (RIF). Serum rosette-inhibiting activity was assessed by a quantitative rosette inhibition test; rosette inhibition was widely distributed among species. Rosette formation with similar temperature requirements, previously reported in a mouse lymphoma carrying membrane-bound heterophile cold hemagglutinin, was readily distinguished from viral hemadsorption by its insensitivity to mouse serum RIF. Although factors influencing rosetting have not been fully elucidated, the rosette formation by mouse lymphoma cells due to viral hemadsorption may provide a unique system in the study of virus-cell interactions.

- 5652 APPEARANCE OF C-TYPE VIRUS-LIKE PARTICLES AFTER CO-CULTIVATION OF A HUMAN TUMOR-CELL LINE WITH RAT (XC) CELLS. (Eng.) Gabelman, N. (Mount Sinai Sch. of Medicine of the City Univ. of New York, New York, N.Y. 10029); Waxman, S.; Smith, W.; Douglas, S. D. *Int. J. Cancer* 16(3):355-369, 1975.

A new cell line, its clone, and the virus isolated from its growth medium are described. A serially propagated cell line (L104) was established by cocultivation of a lung adenocarcinoma (L-1) from a patient with concurrent chronic lymphocytic leukemia and SC, a non-producer rat line. Microscopic examination of the cell line revealed a fibroblast-like and an epithelioid population retained for 50 generations. Karyotype of the L104 cultures revealed predominantly rat-like patterns. About 5% of the cells reacted with HLA antibodies and demonstrated human isozyme patterns. The presence of all or part of human chromosomes 6, 11, 12, 14, 19 and X was indicated by the HLA and isozyme data.

Electron microscopy of L104 cells revealed the presence of C-type particles budding from the cell membranes and in cytoplasmic vacuoles. Virus was not detected in any of the other normal lung, lung tumor or XC cells examined after co-cultivation with XC cells. The particles isolated from tissue culture fluids had the characteristics common to other known mammalian C-type particles and were serologically related to the woolly monkey virus (WMV)/gibbon ape leukemia virus (GaLV) complex. Cross-hybridization between viral [^3H]-DNA transcripts and cellular RNAs from virus-infected cells clearly show the presence of sequences in the L104 cellular RNA related to both the GaLV/WMV group of viruses and rat viruses. Hydroxyapatite chromatography reveals that the primate-related sequences in the viral RNA are indistinguishable from WMV in thermal elution profile. The L104 virus appears to be xenotropic and thus far appears to infect only rat cells. The virus gave positive KC but negative XC assays. Inoculation of whole cells or cell-free supernatants into weanling hamster did not result in either solid tumors or leukemia. Co-cultivation of appropriate cell lines may represent an approach to the detection of latent viruses in human neoplasia.

- 5653 ON TRANSFORMATION ACTIVITY OF ONCORNAVIRUSES ISOLATED FROM CELL LINES RH AND HEP-2. (Rus.) Demidova, A. S. (D. I. Ivanovsky Inst. Virol. USSR Acad. Med. Sci.); Perekrest, V. V.; Mikhailova, G. R.; Guschin, B. V.; Klimenko, S. M.; Tsareva, A. A.; Zhdanov, V. M. *Vopr. Onkol.* 21(3): 50-56; 1975.

The authors describe experiments on the transformation effect of oncornaviruses isolated from cell lines RH and Hep-2 of human tissue cultures on human embryonal kidney cells (KC) and fibroblasts (FC). KC and FC cells were grown in flasks on growth medium 199 with 10% cow serum. Penicillin and streptomycin (100 U/ml) each were added. The oncornaviruses obtained from cell cultures RH and Hep-2 were mixed with the culture fluid of the latter and isolated by centrifuging. The deposit was suspended in 1.5 ml of fluid medium and filtered through micro-pore filters. The filtrates were transferred to unilayers of KC and FC cell cultures. The contact of virus and cell cultures was maintained for 24-72 hrs. No transformation was observed in FC's in 15 experiments. In 16 experimental series with KC's involving 0.2 mg/ml of the carcinogen 20-methyl-cholanthrene with and without the oncornavirus, culture transformation was achieved in two cases. In one experiment, morphologically uniform epithelial cells appeared on the 76th, in another one on the 36th day from the start of the experimental series. Throughout its length, these cells have been able to divide unlimitedly *in vitro* and have lost their contact inhibition, considered to be characteristic of cell transformation. After 15-23 transfers (passages) of these transformed cells, no reduced mitotic activity was noted. Cytogenetic study of these cells (11th passage) during metaphase showed an average of 64 chromosomes representing the picture of a fairly stable heteroploid culture. It

is noteworthy that transformation of KC's occurred two times faster in the presence of virus + 20-methylcholanthrene. Electromicroscopic examination revealed a fairly large number of oncornaviral particles in these cells.

- 5654 ISOLATION OF INFECTIOUS C-TYPE ONCORNAVIRUS FROM HUMAN LEUKAEMIC BONE MARROW CELLS. (Eng.) Nooter, K. (Radiobiol. Inst. TNO, Rijswijk ZH, The Netherlands); Aarssen, A. M.; Bentvelzen, P.; de Groot, F. G.; van Pelt, F. G. *Nature* 256(5518):595-597; 1975.

The isolation of a C-type oncornavirus from a four-year-old patient with a lymphosarcoma which had progressed to a state of lymphoblastic leukemia is reported. Bone marrow cells cultured in liquid suspension in the presence of phytohemagglutinin (10 $\mu\text{l/ml}$) were seeded on top of a 24-hr culture of XC cells. Four days later, conspicuous syncytia were found, the same cytopathogenic effect being found when fresh leukemic bone marrow cells were cocultivated directly with XC cells. Cocultivation of XC cells with bone marrow cells from four normal donors, two patients with acute myeloid leukemia, two with chronic myeloid leukemia, one with aplasia, one with chronic lymphatic leukemia, and one with secondary polycythemia vera did not produce syncytia. The XC cultures which showed a positive cytopathogenic effect released C-type particles, while control XC cultures or mixed cultures of XC cells with normal bone marrow cells did not. Secondary cultures of human embryonic kidney (HEK) and human embryonic fibroblast (FB289) cells replicated the human virus when cocultivated with irradiated XC cells in their second passage after having been in contact with leukemic cells. Indirect immunofluorescence tests with polyvalent rat antiserum to Rauscher murine leukemia virus no. 45 and a goat antiserum to an endogenous C-type oncornavirus isolated from the BALB/c mouse mammary tumor cell line EMT6 showed weak but positive reactions with both antisera. Virus was isolated a second time from the same patient, while in remission, by cocultivating the buffy coat of the peripheral blood with FB289 cells. Indirect immunofluorescence tests gave the same results as with the previous isolate. It was concluded that a C-type oncornavirus was twice isolated from a leukemic child.

- 5655 POSSIBLE ASSOCIATION OF ONCORNAVIRUS TYPE D WITH SOME FORMS OF HUMAN CANCER. (Eng.) Zhdanov, V. M. (Acad. Med. Sci., Moscow, U.S.S.R.); Trushinskaya, G. N.; Mazurenko, N. N.; Zairov, G. K. *Neoplasma* 22(1):13-21; 1975.

The presence of DNA or RNA sequences homologous to nucleic acids of oncornavirus type D was investigated in normal human and animal tissues, and in tissues from patients with various types of cancer using molecular hybridization techniques. The oncornavirus type D was produced by HEp2 cells. Virion RNA was labeled with [^3H]-uridine (25-30 $\mu\text{Ci/ml}$) or with $^{32}\text{PO}_4$, and extracted with phenol from purified and pelleted virions. High molecular wt (60-70 S) RNA was

isolated from appropriate fractions after centrifugation of RNA preparations in sucrose density gradients. Reverse transcriptase was reacted with endogenous template in the presence of actinomycin D and the [³H]-dTTP-labeled product was extracted and precipitated with the addition of carrier calf thymus DNA. RNA admixtures were removed by alkaline hydrolysis, then DNA was neutralized, precipitated and stored. Nucleic acids were extracted from the separated nuclei and cytoplasm of the test cells. DNA preparations were freed from RNA admixtures by alkali hydrolysis, and fragmented by sonication. Nucleic acids were hybridized in the liquid phase. [³H]-labeled viral DNA and [³H]-labeled or ³²P-labeled RNA from normal or cancer tissues was introduced into the hybridization buffer (1000 cpm/sample) and the mixture incubated at 68 C. Analysis of hybridization products was performed by treatment with pancreatic ribonuclease, S-1 nuclease, or fractionation in hydroxyapatite. No sequences homologous to the viral nucleic acids were found in normal human embryo cells, in bovine, porcine, murine or chicken cells, nor in tissues of malignant lymphomas. Positive results were obtained in several hybridization experiments using viral DNA, and DNA and RNA from mammary and ovarian cancers. DNA polymerase activity associated with high molecular weight RNA was revealed in these tumors and in one case of skin cancer. It is concluded that oncornavirus type D, or a closely-related virus, participates in carcinogenesis in some forms of human cancer or, at least, is associated with them.

5656 MOLECULAR HYBRIDIZATION STUDY OF CELLS PRODUCING ONCORNAVIRUSES TYPE D. (Eng.)

Zhdanov, V. M. (Acad. Med. Sci., Moscow, USSR); Mazurenko, N. N.; Demidova, S. A. *Neoplasma* 22(1): 1-11; 1975.

Five human line cells (Hep2, HeLa, RH, Detroit 6, and AO) producing oncornaviruses type D were studied using molecular hybridization of viral and cellular nucleic acids. Repeated sequences of viral genome equivalents were found in nuclear DNA and numerous copies of viral genome were found in the cytoplasm. The nucleotide sequences of the genomes of viruses produced by the cell lines were found to be identical or closely related. The results suggest that the cultures studied produce identical viruses or variants that differ from each other as strains of the same virus. This conclusion is supported by complete hybridization of virion RNA with DNA product deriving from different cell lines and by complete hybridization of DNA product with cell DNA also deriving from different cell lines.

5657 THE INFLUENCE OF INVASION WITH *TRICHINELLA SPIRALIS* ON THE DEVELOPMENT OF RAUSCHER

LEUKEMIA. (Rus.) Trubcheninova, L. P. (Inst. Experimental and Clinical Oncology, Acad. Medical Sciences, Moscow, U.S.S.R.); Chimiskian, K. L.; Ovomyan, G. Sh.; Babichev, V. A.; Svet-Moldavskii, G. Ia. *Vopr. Virusol.* (3):344-348; 1975.

5658 VIRUS ANTIBODY IMMUNE RESPONSE POLYMORPHISMS IN THE FAMILY OF A PATIENT WITH MALIGNANT MELANOMA [abstract]. (Eng.) Buckley, C. E., III (Duke Univ. Med. Cent., Durham, N.C.); Hsia, S.; Siegler, H. F.; Ward, F.; Amos, D. B. *Clin. Res.* 23(1):50A; 1975.

5659 DISTRIBUTION OF THE ISOELECTRIC VARIANTS OF THE PRINCIPAL POLYPEPTIDE (P 30) IN DIFFERENT STRAINS OF MURINE ONCORNA VIRUS. (Fre.) Chuat, J.-C. (Laboratoire d'Hematologie Experimentale, Institut de Recherches sur les Leucemies et les Maladies du Sang, Hopital Saint-Louis, 2, place du Docteur Fournier, 75475 Paris Cedex 10, France); Laprevotte, I.; Boiron, M. *C. R. Acad. Sci. [D] (Paris)* 281(14):1051-1054; 1975.

5660 ISOLATION AND CHARACTERIZATION OF CARCINOGENIC GENES OF ANIMAL VIRUSES. (Dut.)

van der Eb, A. J. (No affiliation given); Graham, F. L.; Abrahams, P. J.; Mulder, C.; Heijneker, H. L.; Warnaar, S. O.; de Vries, F. A. J.; Fiers, W. *Chem. Weekbl.* 72(24):22-26; 1975.

5661 DIFFERENTIATIVE AND VIROLOGIC STUDIES OF TERATOCARCINOMAS *IN VITRO*. (Eng.) Lehman,

J. M. (Univ. Colorado Medical Sch., Denver, Colo.); Speers, W. C.; Swartzendruber, D. E. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 176-177.

5662 TYPE C VIRUS-ASSOCIATED EXPERIMENTAL GRANULOCYTIC LEUKEMIA IN A PRIMATE [abstract].

(Eng.) Kawakami, T. G. (Univ. California, Davis, Calif. 95616); Buckley, P. M.; DePaoli, A.; Coggan, R. J.; Harrold, J. B. *Am. J. Clin. Pathol.* 63(4):599; 1975.

5663 IMMUNOLOGICAL RELATIONSHIP BETWEEN AN ONCORNAVIRUS ISOLATE FROM HEP-2 CELLS AND HUMAN CARCINOMA CELLS [abstract]. (Eng.) Priori,

E. S. (M. D. Anderson Hosp. and Tumor Inst., Houston, Tex.); Ilyin, K. V.; Peterson, C.; Dmochowski, L. *Proc. Am. Assoc. Cancer Res.* 16:43; 1975.

5664 MICROSCOPIC AND PHYSICOCHEMICAL STUDY OF VIRIONS PRODUCED BY AN L CELL SUB-LINE [abstract]. (Fre.) Botis, S. (Departement de Radiobiologie, Centre d'Etude de l'Energie nucleaire,

B-2400-Mol, Belgium); Janowski, M.; Ricciardi-Catagnoli, P.; Sassen, A.; Maisin, J. R. *Arch. Int. Physiol. Biochim.* 83(1):171-172; 1975.

5665 INTRACISTERNAL VIRUS-LIKE PARTICLES IN A SNOW LEOPARD MAMMARY TUMOR [abstract].

(Eng.) Chandra, S. (Mercy Hosp. Med. Cent., Chicago, Ill.); Laughlin, D. C. *Proc. Am. Assoc. Cancer Res.* 16:106; 1975.

5666 ENRICHMENT BY VELOCITY SEDIMENTATION OF HUMAN LEUKEMIC MARROW CELLS PRODUCING VIRAL-RELATED PARTICLES IN CULTURE [abstract].

(Eng.) Mak, T. W. (Univ. Toronto, Ontario Cancer Inst., Canada); Price, G. B.; Miller, R. G.; Potts, T. V.; Housman, D. E. *Proc. Am. Assoc. Cancer Res.* 16:102; 1975.

5667 PRESENCE OF C TYPE VIRUS PARTICLES IN BOVINE LYMPHOCYTE CULTURES WITH PERSISTENT LYMPHOCYTOSIS. PRELIMINARY RESULTS CONCERNING THE FRENCH LIVESTOCK. (Fre.) Guillemain, B. (Laboratoire d'Anatomie Pathologique, Ecole Nationale Veterinaire d'Alfort, Maisons-Alfort, France); Levy, D.; Lasneret, J.; Chevrier, L.; Parodi, A. L.; Boiron, M. *C. R. Acad. Sci. [D] (Paris)* 280(6): 795-798; 1975.

5668 ON THE PRODUCTION OF VIRUS PARTICLES OF DBA/2 MOUSE CULTURED LEUKEMIC CELLS [abstract]. (Jpn.) Tamura, K. (Virus Inst. Kyoto Univ., Kyoto, Japan). *Virus (Tokyo)* 24(3):280; 1975.

5669 STRUCTURE OF SPECIAL ("MINIMAL") FORMS OF A AND C TYPE ONCORNA VIRUSES. (Rus.)

Bykovskii, A. F. (N. F. Gamaleya Inst. Epidemiology Microbiology, Acad. Med. Sci. U.S.S.R., U.S.S.R.); Klitsunova, N. V. *Dokl. Akad. Nauk S.S.S.R.* 224(1): 226-227; 1975.

5670 EXPERIMENT ON THE ISOLATION OF TUMOR VIRUSES FROM CELL CULTURES OF HUMAN NEOPLASMS BY INOCULATION INTO CHICKS. (Cze.) Chyle, M. (128 00 Praha 2, Studnickova 7, Czechoslovakia); Jirasek, A.; Chyle, P. *Česk. Epidemiol. Mikrobiol. Imunol.* 24(1): 54-62; 1975.

See also:

* (Rev): 5401, 5408, 5411, 5420, 5428, 5445, 5446

* (Chem): 5499, 5519, 5559

* (Immun): 5675, 5683, 5690, 5692, 5711, 5719, 5721, 5728, 5733, 5763

* (Path): 5788

* (Epid-Biom): 5866, 5870

- 5671 IMMUNOSURVEILLANCE OF SPONTANEOUS LUNG ADENOMAGENESIS IN MICE. (Eng.) Colnaghi, M. I. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, 20133 Milano, Italy). *Eur. J. Cancer* 11(9):633-637; 1975.

BALB/c mice were injected repeatedly with untreated allogeneic normal lymphoid or lymphoma cells or with syngeneic or allogeneic lymphoma cells (C3Hf, C57BL) blocked by mitomycin-C or by X-rays in order to obtain anti-lymphoma antisera. In comparison to untreated control mice, the lymphoma incidence was decreased in all groups injected with mitomycin-C-treated cells. The lung adenoma incidence was much higher than in the controls in all groups injected with mitomycin-C-treated cells ($P < 0.001$) and in the group injected with untreated C3Hf thymus and spleen cells, ($P < 0.01$). The group injected with C57BL showed only a small increase of lung adenomas. When tested for the number of plaque-forming spleen cells, animals inoculated with mitomycin-C-treated cells revealed a severe immunodepression suggesting a role of the immunosurveillance in adenomagenesis. Also, one group of mice injected with untreated allogeneic normal immunocompetent cells revealed an increased lung adenoma incidence most likely due to a graft versus host phenomenon; this result seems to exclude the fact that a direct carcinogenic effect of mitomycin-C on lung tissue could be responsible for the increased adenomagenesis.

- 5672 SEQUENTIAL EVALUATION OF GENERAL IMMUNE COMPETENCE IN CANCER PATIENTS: CORRELATION WITH CLINICAL COURSE. (Eng.) Eilber, F. R. (Univ. California Sch. Med., Los Angeles); Nizze, J. A.; Morton, D. L. *Cancer* 35(3):660-665; 1975.

An evaluation of general immunologic reactivity was performed in 116 patients with malignant melanoma and in 40 patients with skeletal and soft tissue sarcoma. The median age was 50 yr, and all patients subsequently underwent surgical resections and immunotherapy. Evaluations of nontumor specific general immune reactivity were accomplished with a skin test battery and dinitrochlorobenzene (DNCB) skin tests. An excellent correlation was found between the initial clinical extent of disease and general immune competence. Eighty percent of patients with localized stage I malignant melanoma were DNCB-positive on initial testing, while 64.4% of patients with regional stage II disease, and 36% of those with disseminated stage III melanoma were DNCB-positive prior to therapy. A similar relationship was found in patients with sarcoma; no correlation was found between the initial stage of disease and reactivity to one or more of the common skin test antigens. Analyses of sequential DNCB reactivity after surgical resection revealed a correlation between the variations in immunologic reactivity and the subsequent course of the disease. Ninety percent of those with increased DNCB reactivity remained free of disease, 70% of those with unchanged DNCB reactivity remained disease-free, and 100% of those DNCB-positive patients converting to negative developed recurrence. The systemic suppression of immunologic reactivity was neither a result of a preexisting defect of the immune system, nor the result of malignant replace-

ment of immune effector cells. Although the exact mechanism is not clear, the changes are apparently reversible. The sequential evaluation of DNCB reactivity may be a clinically useful method of monitoring of disease progression.

- 5673 SERUM PROTEINS IN PROSTATIC CANCER. II. EFFECT ON *IN VITRO* CELL-MEDIATED IMMUNOLOGIC RESPONSIVENESS. (Eng.) Ablin, R. J. (1825 West Harrison Street, Chicago, Ill. 60612); Guinan, P. D.; Bruns, G. R.; Sadoughi, N.; Bush, I. M. *Urology* 6(1):22-29; 1975.

An investigation has been made of the effects of sera from patients with prostatic cancer on the *in vitro* migration of WBC and the *in vitro* proliferative response of phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes. Sera from 5 of 7 patients were observed to inhibit the migration of WBC obtained from healthy adult men; there was some correlation observed between the extent of inhibition and increase of the α_2 -globulin fraction of the sera. In only 3 of 17 patients was the PHA-stimulation of the patients' lymphocytes monitored by ^3H -thymidine incorporation) in the presence of their own sera comparable to that achieved using both lymphocytes and sera from healthy normal subjects. Of the remaining 14 patients, 2 were found to have some defect of the lymphocytes themselves that reduced the magnitude of stimulation, 4 had defective sera, and 8 had defects in both lymphocytes and sera. The sera of prostatic cancer patients seem to contain factors that inhibit the migration of WBC and also the proliferative response of lymphocytes to PHA.

- 5674 QUANTITATIVE ESTIMATION OF CYTOTOXIC ACTIVITY OF IMMUNE LYMPHOCYTES USING ^{51}Cr -LABELLED PERITONEAL MACROPHAGES AS TARGET CELLS. (Eng.) Drizlikh, G. I. (N.F. Gamaleya Inst. for Epidemiology and Microbiology, Moscow, U.S.S.R.); Andreyev, A. V.; Kotomina, I. P.; Brondz, B. D. *J. Immunol. Methods* 8(4):383-393; 1975.

Peritoneal macrophages labeled with ^{51}Cr in suspension and cultivated for 48 hr on glass pretreated with poly-L-lysine were used as target cells for determination of the cytotoxic effect of immune lymphocytes. ^{51}Cr release from such target cells from different strains of mice [C57BL/10, C57BL/6, DBA/1, B10.D2(R101), B10.D2(R103), B10.D2(R107), B10.A(2R), C57BL/6(Hz1), and C57BL/6(M505)] was $15.5 \pm 0.8\%$ of the total target cell radioactivity after 20 hr incubation with normal allogeneic lymphocytes. The use of 2% sodium dodecylsulfate ensured 100% solubilization of labeled target cells growing on the glass surface and permitted the cytotoxic effect to be determined by both ^{51}Cr release and the label retained by the intact cells to be measured. The two methods proved to be accurate, reproducible, and in accord with each other as well as with the method of direct cell counting. Determination of released ^{51}Cr enabled the cytotoxic effect of lymphocytes to be measured after four hours incubation with the mac-

rophage monolayer. Six hours of incubation with immune lymphocytes were sufficient to achieve pronounced cytotoxic effects when MC11 ascitic sarcoma cells were used as targets. However, SaI sarcoma cells were much more resistant to cytotoxic effects of immune lymphocytes; pronounced effects were seen only after 18 hr incubation and preliminary centrifugation. The marked differences in the sensitivity of different sarcoma cells thus suggests that the use of tumors as target cells for the study of effector lymphocyte specificity is complicated.

5675 CELL-MEDIATED IMMUNITY TO FRIEND VIRUS-INDUCED LEUKEMIA. I. MODIFICATION OF ¹²⁵IUDR RELEASE CYTOTOXICITY ASSAY FOR USE WITH SUSPENSION TARGET CELLS. (Eng.) Ting, C.-C. (Nat'l. Cancer Inst., Bldg. 8, Room 118, Bethesda Md. 20014); Bushar, G. S.; Rodrigues, D.; Herberman, R. B. *J. Immunol.* 115(5):1351-1356; 1975.

An ¹²⁵IUDR release cytotoxicity assay for *in vitro* measurement of cell-mediated immunity was modified for use with target cells in suspension. An ascitic Friend virus-induced leukemia, FBL-3, was used for immunization of C56BL/6 mice. Inoculation, sc, producing only transient tumor growth, induced immunity as evidence by resistance to ip challenge. Lymphocyte attacker cells were prepared from lymph nodes and spleens of immunized mice. The target cells consisted of ascitic tumor cells or tumor cells adapted to grow in suspension culture and were labeled with ¹²⁵IUDR. The tests were performed either with Linbro tissue culture plates (16-mm wells) and annual harvesting of the cells, or, for larger scale work, with Microtest II plates (6-mm wells) and harvesting by means of an automatic apparatus. After centrifugation of the harvests, pellets and supernatants were counted separately in a gamma scintillation counter. Data obtained in the study were presented as total lysis obtained with immune lymphocytes (IL), total lysis obtained with normal lymphocytes (NL), and net lysis (IL-NL). Study of variables in the test showed that the use of cultured cells as target cells was more satisfactory than the use of ascitic cells, that frequent subculturing of the target cells was important, that there were optimum lengths of time and amounts of label for labeling the target cells, and that there was an optimum time for the incubation of the mixtures of attacker and target cells.

5676 THE MULTICELLULAR (AS OPPOSED TO THE MONOCLONAL) ORIGIN OF THE MURINE MYELOMA. (Eng.) Warner, T. F. C. S. (Mayo Medical Center, Mayo Foundation, Rochester, Minn. 55901); Jager, R. G. *J. Theor. Biol.* 54(2):175-179; 1975.

Evidence is reviewed to support the suggestion that inducible myeloma in the BALB/c mouse may be produced by hybridization of a plasma cell or its precursor and a macrophage. During the activation and transformation of peritoneal macrophages by pristane, mineral oil, or other foreign substances, C-myc viruses are induced, and these act as fusion partners. The myeloma cell results from the fusion

of a transformed macrophage with a B-cell, previously activated by a specific antigen or interaction with an antigen sensitive T-cell, stimulating its differentiation to a plasma cell. This hypothesis is consistent with the specialized antibody secretion and malignant properties of murine myeloma cells.

5677 XENOTRANSPLANTATION OF ESTABLISHED TUMOR CELLS IN CONGENITAL THYMUSLESS "NUDE" MICE. (Ger.) Krause, P. H. (Pathologisches Institut der Medizinischen Hochschule (MHH) D-3000 Hannover Karl-Wiechert-Allee 9, West Germany); Schmitz, R.; Lindemann, M.; Georgii, A. *Z. Krebsforsch.* 83(3):177-186; 1975.

Successful xenotransplantation of five different established tumor cell lines (PV-RS 15 from S.E.-polyoma virus-induced kidney sarcoma in Wistar rats; PV-HS-1 from neonatal polyoma virus-induced sarcoma in hamsters; spontaneous tumor in hamsters; lymphoid cell line from human Burkitt's lymphoma; and a HeLa cell line from human cervical carcinoma) was performed in congenitally athymic "nude" mice by sc, im, ip, or intracardial injection. All cell lines formed progressively and invasively growing tumors at the injection site between the 21st and 28th days. Histologically, the neoplasms resembled the original tumors. The critical cell dose was between 10,000 and 1,000,000 cells. Two established cell lines from normal fibroblasts (3T-3) and kidney (CV-1) failed to grow in "nude" mice. The tumor cell lines induced no tumors in immune-competent mice.

5678 TRANSPLANTATION OF HUMAN CANCERS TO NUDE MICE AND EFFECTS OF THYMUS GRAFTS. (Eng.) Schmidt, M. (Mem. Sloan-Kettering Cancer Cent., New York, N.Y.); Good, R. A. *J. Nat'l. Cancer Inst.* 55(1):81-87; 1975.

The results of xenografting human malignant tissues of various origins to 106 nude mice, and the effects of thymus implantation in these mice are described. Human tumor cell lines included: HUTU-80 isolated from adenocarcinoma of the foregut, HS766 isolated from pancreatic adenocarcinoma, and SK-Mel-5 from melanoma. Thymus glands obtained from neonatal (n), 300 rad-irradiated (xn), or adult (a) hairy littermates were either transplanted sc or injected ip in the following combinations: n-sc, xn-sc, n-ip, a-sc, and a-ip. The mean "age(s) at final assessment" (AFA, a reflection of survival time) was 92 days for all 106 mice. Tumors developed within one week of HUTU-80 inoculation, showing an exponential growth curve, and were capable of reaching half the host size within 60 days. HS-766 produced a solid tumor nodule with a slow growth rate that corresponded to the *in vitro* replication rate. The growth pattern of SK-Mel-5 tumors was slow and linear. In the first implantation experiment, 8 or 10 1- to 2-mo-old nude mice receiving thymus implants (six n-sc and three a-sc) died spontaneously with a mean AFA of 70 days. In a second experiment, nine mice inoculated with HUTU-80 cells at one month were compared with 13 matched controls, which received thymus implants three

weeks later (three n-sc, three xn-sc, two n-ip, three a-sc, and two a-ip). The mean AFA was 87 and 125 days, respectively. Tumors regressed completely in four animals receiving xn-sc, a-sc, or a-ip thymus implants. In the third experiment, four mice received a-sc thymus implants; HUTU-80 inoculations followed by 28-196 days. The mean AFA of these mice was 178 days. No externally detectable tumors developed. These results represent the first instance of successful transplantation of cell lines of human cancer of the foregut and pancreas to the nude mouse. Cell lines of pancreatic carcinoma and melanoma and surgical specimens of melanoma and neoplasms from the pancreas and the colon showed variable growth patterns in this system.

- 5679 ENHANCEMENT OF IMMUNITY AGAINST MURINE SYNGENEIC TUMORS BY A FRACTION EXTRACTED FROM NON-PATHOGENIC MYCOBACTERIA. (Eng.) Lamen-sans, A. (Institut Pasteur, 75015 Paris, France); Chedid, L.; Lederer, E.; Rosselet, J. P.; Gustaf-son, R. H.; Spencer, H. J.; Ludwig, B.; Berger, F. M. *Proc. Natl. Acad. Sci. U.S.A.* 72(9):3656-3660; 1975.

A preparation extracted from nonpathogenic myco-bacteria such as *Mycobacterium smegmatis* and designated interphase material (IPM) was evaluated for antitumor and antiviral activity, hyperreac-tivity to endotoxin, and adjuvant activity and sensitivity to tuberculin. At 100 µg, IPM admin-istered ip was more effective than BCG in protect-ing B6DF1 mice against ip challenge with L-120 leukemia cells (500 cells/mouse). At 30 and 100 µg, IPM had greater activity than BCG in protecting (C57BL x AKR)F₁ hybrid mice against ip inoculations of 10³ syngeneic leukemia cells or 10⁴ Ehrlich ascites carcinoma cells. The mean survival of Charles River CD-1 mice following ip challenge with Columbia SK virus (20 LD₅₀ U, ip) was signifi-cantly increased by IMP given ip or iv in doses of 10, 30, and 100 µg. BCG cells were ineffective when administered ip. IPM (300 µg) from *M. smeg-matis* rendered mice less susceptible to endotoxin (*Salmonella enteritidis*) than did BCG (LD₅₀ of 35 µg versus LD₅₀ of 1 µg). Moreover, IPM admin-istered in Freund's incomplete adjuvant enhanced the humoral and cell-mediated response of guinea pigs to ovalbumin (50 mg/ml), yet induced a weak or negative response to tuberculin (100 or 300 IU).

- 5680 SPECIFIC AFFERENT INTERFERENCE BY ANTI-SERUM OF *IN VIVO* IMMUNITY. (Eng.) Ting, C.-C. (Natl. Cancer Inst., Bethesda, Md. 20014); Herberman, R. B. *Nature* 257(5529):801-802; 1975.

The biological effect of three antisera on the in-duction of *in vivo* immunity to syngeneic tumors was studied. The antisera were antiFriend virus-induced leukemia serum (AFLS) produced by syngeneic immunization of C57BL/6 mice with FBL-5 cells, a Friend virus-induced leukemia; anti-simian virus 40 (SV40) tumor serum (ASVS) produced by immuni-zation of (BALB/c x C57BL/6)F₁ mice with a syn-geneic SV40 tumor; and anti-fetal serum (AFS) pro-duced by immunization of C57BL/c mice with syn-

geneic fetuses. AFLS recognizes Friend type spe-cific, FMR (Friend, Moloney, Rauscher), and cross-reactive fetal antigens. ASVS reacts chiefly with SV40 tumor-associated cell surface antigen, while AFS recognizes only the fetal antigens expressed on fetal or tumor cells. In contrast to 83% pro-tection obtained following immunization of mice with 1 x 10⁴ untreated irradiation FBL-3 cells, 1 x 10⁴ AFLS-treated irradiated cells afforded only 26% pro-tection. This blocking of the immunogenicity by the antiserum was overcome by immunizing with 1 x 10⁵ treated cells. ASVS, AFS, and normal mouse serum had no significant effect on tumor immunity, demon-strating the specificity of the blocking. The mechanism of the blocking by AFLS did not seem to be related to a direct cytotoxic effect on tumor cells, as shown by a lack of protection in normal mice challenged with serum-treated cells. More-over, the interference with *in vivo* tumor immunity was antigenically specific: only serum containing antibodies against the appropriate tumor-associated transplantation antigen was effective. The specific antiserum apparently produces afferent interference with *in vivo* tumor immunity by masking the specific antigenic sites and therefore blocking tumor cell immunogenicity.

- 5681 CELLULAR BASIS FOR THE IMMUNE RESPONSE TO METHYLCHOLANTHRENE-INDUCED TUMORS IN MICE. HETEROGENEITY OF EFFECTOR CELLS. (Eng.) Kearney, R. (Royal North Shore Hosp., St. Leonards, NSW 2065, Australia); Basten, A.; Nelson, D. S. *Int. J. Cancer* 15(3):438-450; 1975.

Immune resistance to methylcholanthrene-induced tumors has two phases, an early specific and a late nonspecific phase. Both phases were found to be T-cell-dependent *in vivo*. Thus, adult thy-mectomized, irradiated, bone-marrow-protected mice (CBA/J, CBA/H/WEHI, and AKR/J) bearing H-1 tumor isografts showed impaired resistance to sc chal-lenge with homologous (H-1) and heterologous (H-3) tumor cells (2-5 x 10⁵). In each case, resistance was restored by injection of thymus cells. *In vitro* analysis of the cellular basis of resistance revealed that different mechanisms were involved in the two phases. The cytotoxic effect of immune spleen cells taken during the early specific phase was inhibited by pretreatment with anti-θ serum and complement and by removal of macrophages. Neither procedure, however, interfered with the cytotoxic potential of immune spleen cells taken during the late nonspecific phase of immunity. Passage of immune spleen cells through rabbit im-munoglobulin G (IgG) anti-mouse immunoglobulin-coated columns (which yielded a T-cell-enriched, B-cell-depleted population) resulted in abroga-tion of cytotoxicity whether the cells were ob-tained during the early or the late phase of re-sistance. The inability of late-phase spleen cells to kill was explicable in terms of B-cell removal since T-cells and macrophages had been shown to be ineffective at that time. In contrast, the failure of column-treated cells from the early phase to kill was found to be due to removal of adherent cells rather than B-cells since cyto-toxicity (1) was abrogated by passage through con-

trol columns coated with rabbit-IgG anti-SRBC antibody which did not retain B-cells and (2) could be restored by addition of immune macrophages (from anti- θ serum-treated spleens). Taken together, these results indicate that the cellular basis of immune resistance to methylcholanthrene-induced tumors is heterogeneous. The early specific phase seems to be mediated by an interaction between T-cells and macrophages; the late non-specific phase, although T-cell dependent in its induction, depends on a different effector mechanism, possibly involving a cell or its product of the B lineage.

- 5682 CELLULAR IMMUNE RESPONSES TO METHYLCHOL-ANTHRENE-INDUCED FIBROSARCOMA IN BALB/c MICE. (Eng.) Bhatnagar, R. M. (Rockefeller Univ., New York, N.Y. 10021); Zabriskie, J. B.; Rausen, A. R. *J. Exp. Med.* 142(4):839-855; 1975.

Several *in vitro* parameters of cellular immunity were examined in BALB/c mice with an experimentally induced fibrosarcoma tumor. The results of capillary migration of spleen cells in high tumor cell dose inoculated mice showed appearance of cellular immune response in the early stages of the tumor growth. As the tumor progressed, the cellular response declined and rapidly disappeared, culminating in stimulation values near the time of the death of these mice. The blastogenic studies also showed early cellular recognition of tumor antigen by mouse spleen cells and whole blood Z(24 hr). After the second day following tumor injection, no blast transformation was noted. However, the results obtained with a lower inoculating tumor cell dose demonstrated an initial cellular recognition on the seventh day. This response gradually disappeared by the 19th day and remained negative up to the time of the death of these mice. Cellular immunity was confirmed by the cytotoxic experiments which showed that the primary cells responsible for cellular reactivity were the immune cells. An interesting finding was the presence of a factor(s) capable of blocking the cytotoxic effect. The nature and mechanism of this blocking factor(s) is under investigation.

- 5683 COMPARISON OF THE ALLOSPECIFIC AND VIRAL-SPECIFIC IMMUNE RESPONSES TO IRRADIATED VERSUS FORMALDEHYDE-FIXED ALLOGENEIC MOLONEY LYMPHOMA CELLS IN CBA MICE. (Eng.) Lamon, E. W. (Karolinska Inst., Stockholm, Sweden); Gatti, R. A.; Kiessling, R.; Fenyö, E. M. *Cancer Res.* 35(4):962-969; 1975.

The relative immunogenicity of the viral and H-2 antigens of living versus formaldehyde-fixed cells were determined, and some of the differences in the immune response to the two antigenic systems were examined. Two groups of adult CBA mice were immunized with 10^7 allogeneic Moloney lymphoma (YAC) cells. These YAC (H-2a) cells, which were either irradiated with 6,000 R (group I) or were formaldehyde fixed (group II), were injected ip at weekly intervals for three weeks. Four days following the last injection, sera and lymphocytes were collected

and tested *in vitro* for activity against either allospecific antigens (H-2d target cells) or viral-specific antigens, namely, Moloney leukemia virus (MLV). Both groups of animals developed measurable cellular and humoral immunity to the virally determined antigens. However, only the animals in group I developed detectable immunity to H-2d. Immune and control lymphocytes were tested in microcytotoxicity tests and by ^{51}Cr release. Antibody was assessed by complement-dependent cytotoxicity, indirect membrane immunofluorescence, virus neutralization, and antibody-dependent lymphocyte cytotoxicity. Group I serum, which had both anti-MLV and anti-H-2 antibodies, was absorbed with either living or formaldehyde-fixed YAC cells. The living cells were able to remove both H-2 and MLV antibodies. On the other hand, the formaldehyde-fixed cells removed no H-2 antibody but were able to remove MLV antibody, although less efficiently than living cells. These data indicate that formaldehyde fixation selectively impaired the H-2 antigens, leaving the viral antigenicity relatively intact. Differences between the immune responses to MLV-determined antigens and to H-2 antigens were demonstrated in many of the parallel *in vitro* tests. These studies indicate that the selective denaturation of antigens by fixation will allow the investigation in further detail of the differences in the immune response to virally determined versus transplantation antigens.

- 5684 GENETIC VARIATION OF *IN VITRO* CYTOLYTIC ACTIVITY AND *IN VIVO* REJECTION POTENTIAL OF NON-IMMUNIZED SEMI-SYNGENEIC MICE AGAINST A MOUSE LYMPHOMA LINE. (Eng.) Kiessling, R. (Dept. of Tumor Biology, Karolinska Inst., S 104 01 Stockholm 60, Sweden); Petranyi, G.; Klein, G.; Wigzell, H. *Int. J. Cancer* 15(6):933-940; 1975.

A comparison was made between *in vitro* lysis of mouse strain A-derived Moloney virus-induced lymphoma YAC-1 cells by normal spleen cells of various semi-syngeneic hybrid mice and *in vivo* rejection of ascites or cultured tumor cells when inoculated into corresponding hybrid mice in parallel tests. For the *in vitro* tests, 2×10^6 spleen cells in F 13-10% fetal calf serum were mixed with 4×10^4 ^{51}Cr -labeled YAC-1 target cells; the mixtures were incubated 12 hr and centrifuged, and the pellets of unlysed cells were measured for radioactivity. Strains of mice which were low-reactive with respect to *in vitro* tests included A, A x A.SW, A x A.By, and A x A.CA, while high-reactive strains included A x C57BL/6, A x C57 leaden, A x C3H, A x CBA, and A x CBA/2. For *in vivo* tests, 10^3 to 10^5 YAC-1 cells were inoculated into the test hybrid mice and outgrowth of tumor was followed for 7 weeks. With an inoculum dose of 10^3 YAC-1 ascites cells, it was found that only 17-33% of the mice in the low-reactive groups survived tumor-free, compared to 67-92% of the high-reactive group which survived tumor-free. When comparable tests were carried out using cultured instead of ascites target cells, it was found that the growth of the YAC-1 line was again dependent on the host genotype, with a similar resistance pattern as obtained with the ascites YAC-1 cells, but with a higher

threshold dose. This was in accord with the previously demonstrated higher sensitivity of the cultured line to the cytolytic effect of spleen cells *in vitro*. In segregating (A x C57BL) x A backcross mice, *in vivo* rejection of YAC-1 cells was found to be H-2 linked. This finding was in line with an earlier backcross analysis of the *in vitro* cytotoxicity and suggested a polygenic control with at least one H-2 linked factor.

- 5685 COMPARISON OF PHYSICAL AND IMMUNOLOGICAL PROPERTIES OF PLASMA MEMBRANES OF TWO MOUSE LEUKEMIA CELL LINES, P388 AND L1210. (Eng.) Chen, K. (Yale Univ. Sch. Medicine, New Haven, Conn. 06510); Tsai, C.; Canellakis, E. S. *Cancer Res.* 35(9):2403-2412; 1975.

A method for the isolation of the plasma membranes of the mouse leukemia cell P388 is described. The method included surface labeling of the cell membrane with ^{125}I . Isolation of membranes consisted of cell homogenization and fractional centrifugation, a key factor being the incorporation of phenylmethylsulfonyl chloride into the medium to inhibit membrane degradation which otherwise would occur in homogenates and in sucrose gradients. Criteria used to define the purity of the preparations included the specific activity of covalently labeled ^{125}I , the specific activity of various enzyme markers, and examination by electron microscopy. The membrane preparations had a specific radioactivity 8- to 13-fold higher than that of the cell homogenate. The protein yield was 1-2%. Specific enzyme activity for 5'-nucleotidase increased nine-fold and that for alkaline phosphatase, 22-fold. The membranes were devoid of succinic dehydrogenase, demonstrating the absence of mitochondria. They also showed a 20% decrease in NADPH-cytochrome *c* reductase and a 40% decrease in glucose-6-phosphate. Electron microscopy showed that the membranes formed small vesicles, and no other cell organelles could be detected. Polyacrylamide gel electrophoresis of ^{125}I -labeled membranes dissolved in SDS-mercaptoethanol revealed by the disc technique a distinctive component of molecular weight 13,000 daltons, but gave poor resolution; the gradient slab technique using 7.5 to 15% acrylamide revealed predominant labeled bands at molecular weights of 85,000 and 13,000 daltons. Coomassie blue staining after electrophoresis of membrane materials on gradient slab gels showed more than 30 bands, the most prominent one of which had a molecular weight of 50,000 daltons; these findings obtained for both P388 and L1210 cells. Rabbit antiserum prepared against P388 and L1210 membranes inhibited the growth of the corresponding cells in the absence of complement. They also showed cross-reactivity to each other but did not affect the growth of HeLa cells. Further, anti-L1210 serum partially inhibited the incorporation of glycine, uridine, and thymidine into the L1210 cells and had similar effects on P388 cells. Corresponding inhibition was obtained with anti-P388 for these cells. It was proposed that antiserum made against plasma membrane proteins, or single antibodies made against specific membrane proteins, constitute good

systems for studying the cytotoxic mechanism and the regulation of cell growth by its plasma membrane.

- 5686 LEUKAEMIC TRANSFORMATION OF F_1 -HYBRID CELLS AFTER INOCULATION OF PARENTAL LEUKAEMIC CELLS. (Eng.) Thiel, E. (Inst. f. Hämatologie d. Ges. f. Strahlen u. Umweltforsch. 8 München 2, Landwehrstrasse 61, West Germany); Baumann, P.; Thierfelder, S. *Blut (München)* 30(6): 277-282; 1975.

An experimental model, the chromosomal aneuploidy in a spontaneous acute lymphatic leukemia, suggested malignant transformation in C57B/L and CBA-T6T6 mice tagged with a T_6 -marker chromosome transformation observed in clinical bone marrow transplantation. Chromosomal analysis of spleen and bone marrow cells of mice inoculated with leukemia (ip with 10^6 cells) revealed a hyperdiploid anomaly in the mitoses of the leukemia cells which altered with time. In 1970, the distribution of chromosomes showed a peak of 43 chromosomes that had shifted by 1972 to 41 chromosomes accompanied by a reduction in mean survival time (MST) from 9-14 days after transplant of the leukemia cells. Anti-lymphocyte serum, cyclophosphamide, or irradiation was required to transfer the leukemia to allogeneic rodents. H_2 -incompatible CBA-T6T6 recipients died after a MST of 12 days. Chromosomal analysis of these mice showed a rapid proliferation of the aneuploid leukemic cells. Xenogenetic transfer to Wistar rats pretreated with anti-lymphocyte serum caused the death of animals by seven days. During the progression of disease, a proliferation of leukemic mouse cells with chromosomal anomaly was observed. Transfers of C57BL-lymphatic leukemia to semiallogeneic F_1 -hybrids also required immunosuppressive treatment. The mean survival time after leukemia inoculation did not differ significantly from that of the parental strain. In addition, a single transfer of C57BL/6 leukemic cells to the semiallogeneic hybrids resulted in a proliferation similar to that found in immunosuppressed allogeneic mice. After 6-7 transfers, mitoses containing both the T_6 -marker chromosome and the karyotypic anomaly were observed. However, the altered mitoses were within low ranges, (averaging 12.7% of all mitoses scored). Thus, transfer of leukemic cells to nonleukemia F_1 -hybrids carrying the T_6 marker chromosome permits the simultaneous classification of mitoses according to their malignant, nonmalignant, and donor host origin.

- 5687 THE DISTRIBUTION AND MOBILITY OF ANIONIC SITES ON THE SURFACES OF BABY HAMSTER KIDNEY CELLS. (Eng.) Grinnell, F. (Southwestern Medical Sch., Dallas, Tex. 75235); Tobleman, M. Q. Hackenbrock, C. R. *J. Cell Biol.* 66(3):470-479; 1975.

Polycationic ferritin, because it can be bound at physiological pH to either fixed or unfixed cell surfaces, was chosen as a ligand for visually determining the distribution and mobility of anionic

sites on the surfaces of cultured baby hamster cells. Suspension-cultured BHK-21-13s cells, collected in logarithmic growth phase by centrifugation and resuspended in phosphate-buffered saline (PBS) at a concentration of 2×10^6 cells/ml, were incubated at room temperature with polycationic ferritin (8 mg/ml) for varying periods of time. The reactions were stopped by addition of 10 vol of PBS and of 2% glutaraldehyde in PBS to give a final concentration of 0.2%. The cells were centrifuged and prepared for transmission electron microscopy by thin-section techniques using osmium tetroxide, uranyl acetate, and lead hydroxide. The observations revealed that anionic sites were distributed over the entire cell surface, with the highest density of sites being located on cell surface microextensions. Following the initial binding of polycationic ferritin to the surface of unfixed cells, the ligand-bound anionic sites redistributed by migrating from the surface of microextensions to the surface of the cell body. In 20 min, this migration resulted in a total clearing of anionic sites from the surface of microextensions, concomitant with the formation of patches of anionic sites on the surface of the cell body. Polycationic ferritin-induced migration and path formation of anionic sites was not prevented by inhibitors of cell metabolism (2,4-dinitrophenol or N-ethylmaleimide), an inhibitor of microtubule-mediated processes (colchicine), or an inhibitor of microfilament-mediated processes (cytochalasin B). However, the ligand-induced redistribution of cell surface anionic sites was prevented by prefixation of the cells with glutaraldehyde. The observation that the highest density of anionic sites was associated with cell surface microextensions was considered especially significant since cell surface extensions may be the initial sites of cell adhesion and various cell-cell interactions. The continued presence of surface anionic sites was not a requirement for the maintenance of microextensions since these structures persisted following removal of the sites from the membrane surface of the microextensions.

- 5688 MEMBRANE FLUIDITY IN TRANSFORMED CELLS AND A POSSIBLE RELEVANCE OF THE MITOTIC SURFACE ALTERATIONS FOR GROWTH. (Eng.) Burger, M. M. (Biocenter, Univ. Basel, Klingelbergstr.70 CH 4056 Basel, Switzerland); Horwitz, A. F.; Hatten, M. E.; Scandella, C.; Mannino, R. J., Jr. *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 230-235.

The relation between concanavalin A (Con A) membrane fluidity in 3T3 mouse fibroblasts, and simian virus 40 (SV40)-transformed cells, and mitotic surface alterations during growth was studied by altering the fatty acid composition of the membrane to a higher or lower transition point. A temperature profile for the agglutination with Con A reflected a sharp increase from 12-18 C for both untransformed and transformed mouse fibroblasts. When elaidate (a fatty acid with a high transition point) was introduced into the fibroblast membrane,

the transition for agglutination was raised to 22 C. The introduction of oleate (low transition point) reduced the transition for agglutination to 7 C. In the transformed cells, the shifts in agglutination were the same. The elaidate increase in transformed cell membranes did not decrease the degree to which these cell agglutinated, nor did untransformed cells increase their degree of agglutination in spite of an increased oleate content. Identical electron spin-resonance spectra and other parameters were observed when 5-, 10-, and 14-doxyl stearate were introduced into transformed and untransformed fibroblasts, suggesting that at least those areas which permit access to the fatty lipid probe did not differ with regard to the fluidity of transformed and untransformed cells. Addition of succinyl-Con A to growing 3T3 fibroblasts inhibited growth at a specific cell density, independent of the initial density, but dependent on the lectin concentration. The cells were arrested in G₁. The authors conclude that succinyl-Con A can arrest cells in G₁ when added at a specific time in the cell cycle, i.e., during the preceding mitosis. The transformed cell surface alteration detected with lectins is temporarily present also during mitosis of untransformed cells. In addition, the authors present a model of their working hypothesis which integrates several of these observations.

- 5689 INHIBITION OF NORMAL HUMAN *IN VITRO* COLONY FORMING CELLS BY CELLS FROM LEUKAEMIC PATIENTS. (Eng.) Morris, T. C. M. (Royal Victoria Hosp., Belfast, U.K.); McNeill, T. A.; Bridges, J. M. *Br. J. Cancer* 31(6):641-648; 1975.

To determine whether failure of colony growth with bone marrow from patients with acute myeloid leukemia might be due to a lack of cells with colony-forming potential or to the production of colony-inhibiting factors by leukemic cells, a study was carried out on the effect of added leukemic cells on the colony growth of normal bone marrow cells. Peripheral blood and bone marrow samples were obtained from nine patients with acute myelomonocytic leukemia and from normal individuals, and excess RBC were removed as required. Cultures were prepared by a double layer technique. Colony-stimulating factor was provided by the inclusion of 5% human spleen or human embryo cell conditioned medium in an Eagle's medium-1.2% agar underlay. Eagle's-0.3% agar medium containing the desired concentrations of bone marrow and leukemic cells was placed over the gelled underlayer, the cultures were incubated for 7 days at 37 C, and colonies which formed were counted with a stereoscopic microscope. Coculture in agar of normal bone marrow cells from different individuals gave granulocyte macrophage colony counts that were expected from counts made when the marrows were cultured separately. Coculture of normal marrow with normal peripheral blood leucocytes caused inhibition of colony growth only when the ratio of peripheral blood to bone marrow cells was on the order of 4:1. Peripheral blood or bone marrow cells from 7 of 9 of the leukemic patients caused a marked reduction in the number of colonies from normal

marrow cells when cultured with them. This inhibitory effect of leukemic cells was found when ratios of leukemic to normal cells were as low as 1:4. Additional evidence that the inhibition of normal colony formation was related to the leukemic process was obtained from follow-up studies on one of the patients whose cells were found to lose the capacity to inhibit normal colony formation during remission and to become inhibitory again on relapse.

- 5690 SUPPRESSION OF SPONTANEOUS *IN VITRO* TRANSFORMATION OF AUTOLOGOUS LEUKOCYTES BY PLASMA FROM CONVALESCENT AND POSTCONVALESCENT INFECTIOUS MONONUCLEOSIS PATIENTS. (Eng.) Chang, R. S. (Sch. Medicine, Univ. California, Davis, Calif. 95616); Spina, C. A. *J. Natl. Cancer Inst.* 55(4): 803-805; 1975.

The ability of plasma from patients with acute infectious mononucleosis (IM) or from convalescent or postconvalescent IM patients to suppress the *in vitro* transformation of autologous leukocytes was tested. All 14 plasma samples from 13 convalescent and postconvalescent IM patients suppressed transformation of autologous leukocytes (cultured at a 20% concentration for three weeks and fed with 20% fetal calf serum for three weeks thereafter). In contrast, only 2 of 8 plasma samples from patients with acute IM suppressed this transformation. All seven patients whose blood was tested both in the acute and convalescent or postconvalescent phases of IM showed either a conversion in transformation suppression status from negative to positive or an increase in the strength of transformation suppression. Thus, recovery from IM appears to be associated with the ability of plasma to suppress the *in vitro* spontaneous transformation of autologous leukocytes.

- 5691 VARIATIONS IN THE FREQUENCY OF FETAL HEMOGLOBIN-BEARING ERYTHROCYTES (F-CELLS) IN WELL ADULTS, PREGNANT WOMEN, AND ADULT LEUKEMICS. (Eng.) Boyer, S. H. (The Johns Hopkins Univ. Sch. Medicine, 720 Rutland Ave., Baltimore, Md. 21205); Belding, T. K.; Margolet, L.; Noyes, A. N.; Burke, P. J.; Bell, W. R. *Johns Hopkins Med. J.* 137(3): 105-115; 1975.

Frequency of fetal hemoglobin-bearing RBC (F-cells) in normal, pregnant, and leukemic subjects was investigated as a guide for use of F-cell assay for investigative and diagnostic purposes. F-cells were identified in venous or capillary blood samples by a microscopic single cell radial immunodiffusion assay. Antisera used for the assay were raised in goats and rabbits against fetal hemoglobin (HbF) which had been purified by column chromatography from the blood of an adolescent boy homozygous for hereditary persistence of fetal hemoglobin. The test samples of RBC were suspended in agarose and placed between a microscope slide and a cover slip which rested on strips of Scotch tape. After removal of the cover slip, HbF antiserum was overlaid, the reaction was allowed to proceed overnight, the cells were disrupted with

gramicidin, and reaction of released HbF with anti-HbF to form pericellular immunoprecipitates was observed in microscopic dark fields. As little as 2% of the total hemoglobin in an RBC could be detected. In normal adults, the F-cell frequency varied from 1 F-cell/25 RBC to 1/6800, and the mean HbF per F-cell ranged from 14 to 28% of the mean cell hemoglobin. For a given individual, F-cell lifetimes were probably similar to those of other RBC. F-cell frequencies were briefly but substantially increased in many women during midpregnancy. In some women, 3-7-fold increases in F-cell frequency were observed during the 23rd-31st weeks of gestation. These increases in F-cell frequency arose from selective alterations in maternal erythropoiesis and not from transplacental bleeding from the fetus. Substantial increases in F-cell frequency also occurred in most adults with acute leukemia. In both pregnancy and leukemia, F-cell contributions of HbF were sufficient to account for modest elevations found in hemolysate HbF levels.

- 5692 STUDIES OF LYMPHOCYTE STIMULATION BY INTACT TUMOR-CELL AND SOLUBILIZED TUMOR ANTIGEN. (Eng.) Dean, J. H. (Litton Bionetics, Inc., Kensington, Md. 20795); McCoy, J. L.; Lewis, D.; Appella, E.; Law, L. W. *Int. J. Cancer* 16:465-475; 1975.

The ability of a microculture lymphocyte transformation assay to detect host-specific reactivity and cell mediated immune reactivity against intact tumor-specific antigen (TSA) on simian virus 40 (SV40)-induced tumor cells in mixed lymphocyte/tumor-cell cultures (MLTC) was evaluated. BALB/c mice were rendered immune to mKSA (a syngeneic SV-40 induced sarcoma) by sc injection of 10^6 mKSA-TU5 cells. Spleen cells from immune mice were examined for tumor-cell neutralization in the Winn assay and *in vitro* by lymphocyte stimulation (LS) assays. The specificity of the microculture (200 μ l) LS assay was determined by using spleen cells from immune and nonimmune mice and mice immunized against Adj-PC5 (a mice mineral oil-induced plasmacytoma), and KA-31 (Kirsten virus-induced sarcoma) tumors. The Winn assay demonstrated that mKSA-ASC cells mixed with spleen cells from TU5 immune mice in a ratio of 100:1 neutralized the tumor-inducing capacity of mKSA-ASC cells, and indicated that the immunization regimen was effective in sensitizing spleen cells of syngeneic mice. BALB/c immunized mice completely resisted challenge of 5×10^4 mKSA-ASC cells. In the LS assays with crude soluble extract preparations, good stimulation of TU5 immune lymphocytes was observed with various concentrations of the papain-solubilized mKSA antigen preparation (0.1-25 μ g/well, optimal effect was observed at 1 μ g/well). No stimulation of spleen cells from Adj-PC5 or KA-31 immune mice was noted nor did the papain-solubilized antigen preparation from BALB/c spleen cells provide stimulation. MLTC assays demonstrated that spleen cell/tumor cell ratios of 5:1 to 20:1 affected good stimulation of sensitized cells. No appreciable stimulation of normal spleen cells was observed. Good stimulation of TU5 immune lympho-

cytes was obtained with mitomycin-C blocked TU5 cells. No stimulation was seen when spleen cells of BALB/c mice immunized with Adj-PC5 or KA-31 cells were used, suggesting that the immune recognition events were specific for TSA of the SV 40-induced tumor. Thus, the assays afford a method for demonstrating the presence of TSA and for monitoring further purification procedures.

5693 IMMUNOLOGICAL CROSS-REACTIVITY BETWEEN BASIC PROTEINS OF MYELIN AND CANCER. I. LYMPHOCYTE TRANSFORMATION STUDIES IN IMMUNIZED GUINEA-PIGS. (Eng.) Coates, A. S. (Royal Melbourne Hosp., Victoria, 3050, Australia); Carnegie, P. R. *Clin. Exp. Immunol.* 22(1):16-21; 1975.

To confirm previous evidence by the macrophage electrophoretic migration (MEM) assay for antigenic cross-reactivity between a basic protein of human tumor (TBP) and a basic protein of human myelin (MBP), a study was made using similar human antigens in a more conventional test system, namely, lymphocyte transformation on exposure to antigen. The MPB was obtained and purified by established procedures of ion exchange and gel filtration chromatography. The TBP was prepared as a mixture of proteins, using human rectal carcinoma and cholangio-carcinoma as sources. Normal rectal tissue preparations, obtained by similar procedures, and calf thymus histone, were used as control proteins. Guinea pigs were immunized i.d. in the foot-pads with antigen plus Freund's complete adjuvant, and spleen cell suspensions were prepared from the immunized animals. Transformation of cultures consisting of 5×10^6 viable spleen cells exposed to varying amounts of added test antigens was assessed on the basis of uptake of tritiated thymidine, which was added 6 hr before the end of a 72 hr period of culture. It was found that lymphocytes from guinea-pigs injected with TBP of human cancer tissue showed significant transformation on exposure to MBP and, conversely, that lymphocytes from guinea-pigs injected with MBP showed significant transformation on exposure to TBP. Lymphocytes from guinea-pigs injected with normal tissue extract (NTE) yielded, on exposure to MPB, results which were intermediate between those for control guinea-pigs and those injected with TBP, indicating partial cross-reactivity of NTE with TBP. No cross-reactivity between calf thymus histone and MBP, TBP or NTE could be demonstrated by lymphocyte transformation. Lymphocytes from control non-injected guinea-pigs did not transform on exposure to either antigen. The findings thus obtained with the lymphocyte transformation test system supported those previously obtained with the MEM assay.

5694 LYMPHOCYTE AND MACROPHAGE ADENYL CYCLASE ACTIVITY IN ANIMALS WITH ENHANCED CELL-MEDIATED RESISTANCE TO INFECTION AND TUMORS. (Eng.) Hroller, M. J. (Palo Alto Medical Res. Foundation, Palo Alto, Calif. 94305); Remington, J. S. *Cell Immunol.* 19(2):349-355; 1975.

Because cyclic AMP has been associated with the inhibition of lymphocyte cytotoxicity, the *in vivo*

adenyl cyclase activity of lymphocytes and macrophages was studied in *Toxoplasma*-infected female BALB/c mice in which the efferent limb of the cell-mediated immune response had previously been found to be activated. Peritoneal lymphocytes and macrophages and splenic lymphocytes were harvested from four groups of mice: mice chronically infected with *Toxoplasma* and uninfected control mice, and *Toxoplasma*-infected and uninfected mice bearing isogeneic bladder tumors. Resistance of infected mice to this tumor had been demonstrated in an earlier study. Baseline adeny cyclase activity, as well as prostaglandin E_1 - and NaF-stimulated enzyme activity, was significantly lower in peritoneal and splenic lymphocytes from infected mice compared with uninfected mice. Similar results were obtained with peritoneal macrophages. Both splenic and peritoneal lymphocytes from tumor-bearing mice had lower baseline and stimulated adeny cyclase activities than did corresponding lymphocytes from nontumor-bearing mice. Similarly, in *Toxoplasma*-infected, tumor-bearing mice, adeny cyclase activity in lymphocytes was consistently lower than in lymphocytes from uninfected, nontumor-bearing mice. There was no evidence that both infection and tumor led to an additive decrease of lymphocyte adeny cyclase activity. The proportion of B cells in tumor-bearing mice was sharply decreased compared with the number in *Toxoplasma*-infected mice and uninfected controls. The number of T cells was comparable to that in *Toxoplasma*-infected mice. The data suggest that production of cyclic AMP by lymphocytes is inhibited with the activation of certain cell-mediated immune functions.

5695 GENES ASSOCIATED WITH LEUKOCYTE PRODUCTION IN MICE. (Eng.) Chai, C. K. (Jackson Lab., Bar Harbor, Maine 04609). *J. Hered.* 66(5):301-308; 1975.

A quantitative genetic study involving a selective breeding experiment for leukocyte count differences was described. The mice used to begin the directional selection were derived from a hybrid population; lines selected for high leukocyte count (HLC), low leukocyte count (LLC), and a random line (RLC) were maintained. Counter selections were made in each of the selected lines at the 11th and 14th generations, i.e. selected for low leukocyte count in the HLC lines and for high leukocyte count in the LLC lines. Crossbreeding was made at the 21st generation of selection, and F₁ hybrid and backcross generations were produced. The general trend indicated that the counts of LLC mice showed no additional decrease after six generations, while the leukocyte counts in HLC mice continuously rose. A sharp rise in the mean total count in the HLC line occurred following inbreeding with the 22nd generation. The mean counts for HLC females appeared to be greater than for males. The remaining counter-selective lines drifted toward intermediate values, and dominance of low leukocyte count over high leukocyte count was suggested. Analysis for variance within each line for leukocyte count showed highly significant differences between coat colors; such differences are believed to result from generation differences

in total leukocyte count and variations in coat color gene frequencies. Crossbreeding of the HLC and LLC lines illustrated the dominance effect of genes for low counts over those for high counts. Methods of using marker genes were developed to search for individual genes distribution on different chromosomes. The directional selection resulted in two major lines of mice with seven-fold differences in total leukocyte counts, and revealed the genetic potential of leukopoiesis.

- 5696 NATURAL OCCURRENCE OF LYMPHOCYTES SHOWING CYTOTOXIC ACTIVITY TO BALB/c RADIATION-INDUCED LEUKEMIA RL δ 1 CELLS. (Eng.) Sendo, F. (Viral Leukemia and Lymphoma Branch, Natl. Cancer Inst., Bethesda, Md. 20014); Aoki, T.; Boyse, E. A.; Buafu, C. K. *J. Natl. Cancer Inst.* 55(3):603-609; 1975.

Spleen cells from untreated young male and female C57BL/6 and C58 mice and of male C3H/He mice were investigated for cytotoxic activity *in vitro* against BALB/c X-radiation-induced leukemia RL δ 1 cells by ^{51}Cr -releasing lymphocyte-mediated cytotoxicity (LMC) tests. Old mice of these strains lacked LMC activity in contrast to the young mice. Spleen cells from male and female AKR, BALB/c, and DBA/2 mice, and from female C3H/He mice had no appreciable LMC activity. The proportion of active cells in spleens from young (C57BL/6 x BALB/c) F_1 or reciprocal hybrid mice was higher in females than in males. The specificity of the LMC reaction of RL δ 1 cells, determined by LMC inhibition assays, was somewhat different from that of previously reported serologic X.1 tests. Thus the antigen detected by LMC has been tentatively designated X.1'. The main effector cells in this system were uncharacterized cells not adherent to glass surfaces or nylon-wool columns. These findings in RL δ 1 leukemia extend the evidence for the presence of naturally occurring LMC. With the single unexplained exception of strain C3H/He, the LMC activity against RL δ 1 cells, exhibited by untreated mice of various strains, corresponded with a previous classification of mouse strains immunologically as X.1 responders or as X.1 nonresponders according to their ability to reject X.1-positive leukemia cells.

- 5697 IMMUNE RESPONSE TO A SYNGENEIC MAMMARY ADENOCARCINOMA. II. *IN VITRO* GENERATION OF CYTOTOXIC LYMPHOCYTES. (Eng.) Kuperman, O. (Immunobiology Res. Center, 1150 University Ave., Univ. Wisconsin, Madison, Wis. 53706); Fortner, G. W.; Lucas, Z. J. *J. Immunol.* 115(5):1277-1281; 1975.

A method is described for consistent *in vitro* generation of cytotoxic cells by incubating Fischer 344 rat spleen cells on monolayers of a syngeneic 7,12-dimethylbenz(a)anthracene-induced mammary adenocarcinoma. The ascitic form of this tumor, line 13762A, was adapted for growth in monolayer cultures (MTM). Lymphoid cell suspensions were obtained by pressing pieces of spleen through stainless steel mesh, followed by removal of red blood cells with Tris-buffered NH_4Cl . *In vitro* sensitization was accomplished by placing 10^6 MTM cells in gelatin-coated 60-mm plastic Petri dishes, irradiating the

confluent monolayer which developed, and adding 30×10^6 syngeneic spleen cells in medium containing 10% agamma globulinemic horse serum (AGHS). At suitable intervals, cells are collected from the monolayers, and lymphocytes are separated from tumor cells by sedimentation on a modified Ficoll-Isopaque gradient, the cell pellet containing the lymphocytes. Microcytotoxicity assay of the lymphocyte fraction is carried out with MTM target cells, based on ^{86}Rb incorporation by the MTM cells which remain after incubation with the effector lymphocytes. When unprimed lymphocytes were placed on the irradiated MTM cells and removed at daily intervals, it was found that cytotoxicity was detectable in low amounts on day 2 and was still increasing on day 5, the last day on which tests were made. Cytotoxic cells generated *in vitro* against MTM cells appeared specific for MTM cells, since they were unreactive against cells of another Fischer mammary tumor line (R 3230AC) and of Fischer skin fibroblasts. Further, it was shown that MTM cells were not uniquely susceptible target cells being destroyed by a nonspecifically activated cell, since lymphocytes sensitized on syngeneic fibroblasts were lytic towards fibroblast target cells, but incapable of lysing either MTM or HeLa target cells. From kinetic studies, it was found that the rate of target lysis by *in vitro* generated cells was linear for about 40 hr and extrapolated to zero time intercept. Blocking activity of immune sera could also be demonstrated with the system by substitution of sera from tumor-bearing rats for AGHS in the sensitization phase.

- 5698 SUPPRESSION OF THE IMMUNE-RESPONSE BY α -FETOPROTEIN. II. THE EFFECT OF MOUSE α -FETOPROTEIN ON MIXED LYMPHOCYTE REACTIVITY AND MITOGEN-INDUCED LYMPHOCYTE TRANSFORMATION. (Eng.) Murgita, R. A. (Mayo Med. Sch., Rochester, Minn.); Tomasi, T. B., Jr. *J. Exp. Med.* 141(2):440-452; 1975.

Effects of mouse α -fetoprotein (AFP) on mixed lymphocyte reactivity and mitogen-induced lymphocyte transformation were studied in CBA/J and BALB/c mice. AFP was isolated by antibody-agarose affinity chromatography followed by polyacrylamide gel electrophoresis. One-way mixed lymphocyte reactions were performed by culturing 5×10^6 stimulator spleen cells (BALB/c treated with 25 μg mitomycin C/ml) with 2×10^6 responder (CBA/J) cells. The two cell lines were treated with 4.5 and 9.0 $\mu\text{g}/\text{ml}$ phytohemagglutinin (PHA) and 4.5 and 9.0 $\mu\text{g}/\text{ml}$ concanavalin A (Con A), or with lipopolysaccharide (LPS, 15.7, 31.25, and 62.5 $\mu\text{g}/\text{ml}$). AFP, both in the isolated form and as it occurs in the amniotic fluid (MAF) of pregnant HA/IRC mice, suppressed the mitogenic effects of PHA, Con A, and LPS on mouse spleen cells. It inhibited allogeneic lymphocyte stimulation in the mixed lymphocyte reaction. Dose-response experiments demonstrated that AFP suppression of the response to mitogens and to allogeneic cells diminished linearly with inhibitory activity still evident at 1 $\mu\text{g}/\text{ml}$. AFP had no significant effect on cells in media alone, and cell viabilities of cultures containing MAF or AFP

showed no change from control cultures. Unfractionated MAF also stimulated lymphocyte reactions *in vitro*, which was particularly evident in the mixed lymphocyte reaction. Dialysis partially removed this augmenting activity. Mouse transferrin added to cultures had a stimulatory effect, while albumin was slightly suppressive at 200 µg/ml, but not at 100 µg/ml or lower. The suppressive activity of MAF is apparently due to AFP, while the stimulatory activity is due to low molecular weight factors and to transferrin.

5699 PROTEASE ACTIVITY OF NORMAL AND PHA STIMULATED HUMAN LYMPHOCYTES. (Eng.) Grayzel, A. I. (Montefiore Hosp., Bronx, N.Y. 10467); Latcher, V. B.; Lazarus, G. S. *Cell. Immunol.* 18 (1):210-219; 1975.

An assay measuring the release of trichloroacetic acid-soluble radioactive peptides from ³H acetylated casein or hemoglobin was used to demonstrate that human peripheral blood lymphocytes contain a number of proteases, including cathepsin D, a neutral serine protease(s) inhibited by diisopropylfluorophosphate and N-α-tosyl-L-lysyl chloromethyl ketone (TLCK), and probably a thiol protease(s) as well. One of the neutral proteases was bound to the surface of lymphocytes but was not secreted into the medium; this surface protease was not inhibited by TLCK. Under conditions that did not profoundly inhibit protein synthesis, TLCK inhibited the blastogenic response of lymphocytes to phytohemagglutinin (PHA) and inhibited the total extractable proteolytic activity of lymphocytes by approximately 5%. Although an increase in the activity of a specific proteolytic enzyme might be associated with blastogenesis, the data do not support the hypothesis that normally occurring lymphocyte proteases increase during PHA-induced transformation. The finding of a membrane-bound neutral protease is of interest since a serine protease, not inhibited by TLCK, that converts plasminogen to plasmin has been detected in the medium of cells transformed by oncogenic viruses.

700 FUNCTIONAL ACTIVITIES OF ROSETTE SEPARATED HUMAN PERIPHERAL BLOOD LEUKOCYTES. (Eng.) Bean, J. H. (Dept. Immunology, Little Bionetics, Inc., 16 Nicholson Lane, Kensington, Md. 20795); Silva, S.; McCoy, J. L.; Leonard, C. M.; Cannon, G. B.; Liberman, R. B. *J. Immunol.* 115(5):1449-1455; 1975.

The distinctive properties of human T lymphocytes to form rosettes with unsensitized sheep erythrocytes (E) and of B lymphocytes and monocytes to form rosettes with E sensitized with antibody plus complement (EAC) were used as the basis for methods of isolating human T and non-T cell subpopulations from normal peripheral blood leukocytes (PBL). Rosettes containing the T cell population were separated from a mixture of E and PBL by fractional centrifugation on a Ficoll-Hypaque (FH) gradient. The E rosette-forming cells (E-RFC) located in the pellet and the non-rosetted cells located in the interphase were harvested and each was washed with PBS to release attached E and to yield E-RFC enriched and E-RFC

depleted fractions, resp. On the average, 59% of input PBL was recovered as E-RFC enriched fraction, 28% as E-RFC depleted fraction. EAC rosettes were isolated from the E rosette depleted population by addition of EAC to E rosette depleted PBL, followed by fractional centrifugation on FH to yield a pellet of EAC-RFC and an interface of so-called null cells. The different cell subpopulations were then tested for surface antigen characteristics and various functional activities. Fluorescent antibody staining showed that anti-Ig staining cells concentrated in the E-RFC depleted subpopulation and were markedly depleted from the E-RFC enriched subpopulation. With respect to mitogen induced reactivity, E-RFC responded to PHA, Con A, allogeneic leukocytes, and PPD at higher levels than unseparated PBL, while E-RFC depleted, EAC-RFC, and null cells showed only low responses. A staphylococcal antigen preparation, however, triggered lymphoproliferative reactivity in all subpopulations. ⁵¹Cr release lymphocyte cytotoxicity against human lymphoid F-265 target cells was found in the E-RFC and null cell fractions, but was not observed with the EAC-RFC subpopulation. It is proposed that the methods described should prove useful in assessing the levels of functional T lymphocytes and non-T cells in the blood of patients with various diseases, particularly immunodeficiency syndromes and cancer.

5701 CHEMOTAXIS OF LYMPHOBLASTS. (Eng.) Russell, R. J. (Dept. Bacteriology and Immunology, Univ. of Glasgow, Western Infirmary, Glasgow G11 6NT, Scotland); Wilkinson, P. C.; Sless, F.; Parrott, D. M. V. *Nature* 256(5519):646-648; 1975.

The migration of lymphoblasts was examined in Boyden chambers. Lymphocytes were derived from either human cell lines maintained in continuous culture or blast cells from the lymph nodes of CBA mice, with or without deliberate sensitization with antigen or following exposure to oxazolone. Locomotion and chemotaxis were measured by the micropore filter technique. The leading front cells in a population of mouse lymphoblasts required three hours to migrate toward a strong chemoattractant while human blood monocytes required only two hours to migrate the same distance in the same filters. Cells from seven human lymphoblast cell lines varied considerably in their random unstimulated migration and in their response to chemoattractants. All lines migrated further in the presence of endotoxin-activated plasma; most cells showed an enhanced response to casein. When the absolute concentration and the gradient of the chemoattractants were varied above and below the filter, the rate of lymphocyte locomotion in the absence of a gradient varied with the chemoattractant concentration. Lymphocytes migrating in a positive gradient penetrated deeper into the filter than would be expected on the basis of a concentration-dependent random migration alone; conversely, those migrating in a negative gradient did not penetrate as deeply as would be expected by random migration alone. These results demonstrate that the locomotion response of human lymphoblasts to activated plasma is chemo-

kinetic and chemotactic. Lymphocytes from the auricular nodes of mice sensitized with oxazolone were more motile than unsensitized cells, and usually showed considerable random motility in the absence of any chemoattraction. In 2 of 3 experiments, oxazolone-stimulated blast cells failed to show a chemotactic response, suggesting that blast cells obtained after contact sensitization show a form of locomotion that is unrestrained by the action of microtubules. Thus, blast-transformed lymphocyte populations vary in their locomotor response to chemoattractants more than do neutrophil or macrophage populations.

- 5702 REGULATORY SUBSTANCES PRODUCED BY LYMPHOCYTES. II. LYMPHOTOXIN IN THE RAT. (Eng.) Namba, Y. (Yale Univ. Medical Sch., New Haven, Conn. 06510); Waksman, B. H. *J. Immunol.* 115(4):1018-1022; 1975.

Rat lymphotoxin (LT), a soluble mediator which kills L cells (mouse fibroblasts) within 48 hr, was partially purified by conventional protein fractionation procedures from the culture supernatants of rat lymph node cells. The cells were stimulated with ovalbumin *in vivo* and rechallenged with the same antigen *in vitro*. The elution pattern of DEAE-cellulose chromatography showed a neutral or slightly basic protein which was inactivated at 60°C. Its molecular weight was estimated by Sephadex gel filtration to be approximately 9×10^4 daltons. Partially purified LT showed single hit kinetics. It also inhibited L cell proliferation at low concentration without significant killing effect. The heat inactivation curves of both cytotoxic and proliferation inhibitory activities were the same, suggesting that these two activities may be caused by the same molecule. However, there was almost no detectable effect on the DNA synthesis of rat lymph node cells stimulated with phytohemagglutinin (PHA), suggesting that lymphocytes, at least those which respond to PHA, are rather resistant to LT. It is suggested that activities described as "proliferation inhibitory factor" and "cloning inhibitory factor" by others may represent the activity of dilute LT. The "inhibitor of DNA synthesis" was shown to be distinct in molecular character, range of target cells, and target cell kinetics from LT.

- 5703 CONCURRENT INHIBITION BY CHLORPROMAZINE OF CONCAVALIN A-INDUCED LYMPHOCYTE AGGREGATION AND MITOGENESIS. (Eng.) Ferguson, R. M. (Univ. Minnesota Hosp., Minneapolis, Minn. 55455); Schmidtke, J. R.; Simmons, R. L. *Nature* 256(5520):744-745; 1975.

To obtain evidence that clustering of lymphocytes by concanavalin A (Con A), as well as binding of Con A to lymphocytes, may constitute a necessary prerequisite for mitogenic induction of blast formation, studies were carried out on the possible superimposed effect of the surface membrane-active drug, chlorpromazine (CPZ). Concentrations of CPZ > 0.005 mM totally inhibited the uptake of [3 H]-thymidine by cultured C3H-HeJ mouse spleen cells. The results were not due to toxicity of

the CPZ since concentrations ≤ 0.05 mM had no effect on viability. If, however, an inhibitory concentration of CPZ (0.01 mM) was added 24 hr after addition of Con A, the CPZ showed no effect. This experiment provided additional proof of viability since [3 H]-thymidine incorporation in response to Con A proceeded unaltered in the presence of the drug. Furthermore, the inhibitory effect of the drug seemed not to derive from inhibition of DNA synthesis since, once the Con A-induced intracellular message had been sent and the lymphocyte was committed to respond, the addition of the drug had no effect on the subsequent blastogenic response. Con A-induced lymphocyte aggregation was inhibited by CPZ at concentrations equal to that which inhibited blastogenesis. Added to cultures 12 hr after Con A, however, 0.01 mM CPZ did not disperse already formed clusters. Results of studies on binding of [3 H]-labeled Con A showed that the mechanism of action of CPZ was not inhibition of binding of Con A. Lack of effect of addition of 5 or 10 mM Ca^{2+} to the culture medium showed that the mechanism was also not related to the known Ca^{2+} -blocking activity of CPZ. Further, the known CPZ-inhibition of adenylyl cyclase activity or of production of GMP in different tissues did not appear to be involved. It is suggested that by inhibiting the formation of clusters in Con A-stimulated lymphocyte cultures, CPZ removes the opportunity for the cell-cell interaction which may be essential to blastogenesis. Whether aggregation and blastogenesis are a manifestation of a common lactic acid-induced lymphocyte membrane perturbation or whether each is an independent consequence of mitogen binding remains unknown.

- 5704 LYSOSOMAL ENZYMES IN NORMAL AND CHEDIAK-HIGASHI BLOOD LEUKOCYTES. (Eng.) Kimball, H. R. (Natl. Inst. of Health, Bldg. 10, Room 11N23; Bethesda, Md. 20014); Ford, G. H.; Wolff, S. M. *J. Lab. Clin. Med.* 86(4):616-630; 1975.

Particulate and supernatant fractions isolated from granulocytes of patients with neutropenic Chediak-Higashi syndrome (CHS) were compared with corresponding fractions of normal subjects with respect to lysosomal enzyme activity, and granule fractions also compared with respect to sensitivity to lysosome-disruptive agents. The granulocytes were isolated from heparinized venous blood by a modification of a Ficoll-Hypaque gradient which gave an upper band containing predominantly lymphocytes and a pellet containing erythrocytes and granulocytes. Erythrocytes were removed from granulocytes by osmotic lysis. Disruption of granulocytes was performed by a modified sucrose lysis method. Heparin was essential for satisfactory lysis and subsequent granule separation. Three fractions were obtained: nuclei, granules, and postgranular supernatant (PSG). Assays for all enzymes except muramidase were carried out in the presence of 0.1% Triton X-100 to achieve disruption and solubilization of leukocyte homogenates and fractions. Since Triton X-100 interfered with muramidase determinations, preparations assayed for this enzyme were disrupted by freezing and thawing. The intracellular distrib-

ution of acid phosphatase (p-nitrophenylphosphate substrate) and of alkaline phosphatase (α -glycerophosphate substrate), myeloperoxidase, and muramidase showed a shift of activity into the PSG fraction of CHS granulocytes. With respect to specific activity, alkaline phosphatase activity was 2-fold greater in the granulocyte lysates of CHS cells than in those of normal cells, while specific activities of myeloperoxidase and β -glucuronidase were lower in CHS granulocytes than in normal granulocytes. Lysosomal enzyme distribution and content were similar in CHS and normal mononuclear cells, a finding consistent with the lack of any known functional abnormalities attributable to these cells. Finally, isolated CHS granules were not more sensitive to the lysosome-disruptive agents vitamin A, progesterone, or etiocholanolone than were normal granules.

5705 PRODUCTION OF A SERINE-PROTEASE WITH MACROPHAGE MIGRATION-INHIBITORY FACTOR ACTIVITY BY VIRUS-TRANSFORMED CELLS AND HUMAN TUMOR CELL LINES. (Eng.) Poste, G. (Dept. Experimental Pathology, Roswell Park Memorial Inst., Buffalo, N.Y. 14263). *Cancer Res.* 35(9):2558-2566; 1975.

This work confirms and extends a previous report that 3T3 cells transformed by SV40 release macrophage migratory inhibitory factor (MIF). Cultured cells which were studied included BALB/c mouse 3T3, 3T3 transformed by SV40 (SV3T3), baby hamster kidney (BHK), BHK transformed by polyoma virus (Py-BHK) or by Rous sarcoma virus (RSV-BHK), mouse embryo fibroblasts, hamster embryo fibroblasts, human peripheral lymphocytes, and a wide variety of human tumors and diploid cells. Culture medium supernatants tested for MIF consisted of fresh medium added to the cell cultures 18-24 hr before harvesting. Guinea pig peritoneal macrophages and lymphokine-sensitive human lymphocyte line (RPMI-788) were used as target cells in different assays for MIF. Release of plasminogen activator by cultured cells was identified by measuring the ability of cells or cell-free supernatants to release ^{125}I -labeled fibrinopeptides from ^{125}I -labeled fibrinogen. Fractionation of cell-free supernatants was performed in separate experiments by ultrafiltration using Amicon Diaflo membranes and by chromatography on Sephadex G-75 columns. It was found that SV3T3, Py-BHK, RSV-BHK, and a range of neoplastic human cell lines release MIF affecting macrophages and lymphocytes. Similar MIF activity was not detected in supernatants from 3T3, BHK, or a variety of human diploid cell strains. Results of fractionation studies showed substantial similarities between the tumor-released MIF and that produced by mitogen-activated human peripheral lymphocytes. MIF released by SV3T3 cells was inhibited by pancreatic and soybean inhibitors and by *p*-aminobenzenesulfonamide, all of which inhibit trypsin-like enzymes, but not by other trypsin inhibitors or by inhibitors of chymotrypsin-like enzymes. Diisopropyl fluorophosphate, a specific inhibitor of serine esterases, effectively inhibited the MIF activity of SV3T3 supernatants, indicating that the MIF was a serine-protease. Comparison of MIF produced by SV3T3 cells with a serine-protease plasminogen ac-

tivator released by the same cells indicated that the latter was more heat labile and had a more heterogeneous elution profile after chromatography on Sephadex G-75. The possibility is suggested of a role of MIF in causing proteolytic modification of the surface properties of tumor cells and in altering cell-mediated immune responses to neoplastic cells.

5706 TRANSFORMATION ANTIGENS ON STIMULATED LYMPHOCYTES. (Eng.) Bluming, A. Z. (N. Engl. Med. Cent. Hosp., Boston, Mass.); Lynch, M. J.; Kavanah, M.; Khirya, R. *J. Immunol.* 114(2):717-721; 1975.

Human blood lymphocytes from 28 healthy adults (ranging from 19-28 yr old) were measured for their ability to recognize transformed, autologous lymphocytes as assessed by ^3H -thymidine incorporation. The stimulator lymphocytes (0.3×10^6 viable cells/ml) were incubated with phytohemagglutinin (PHA, 2.5 μg) for 72 hr, and then treated with mitomycin C (19.2 $\mu\text{g}/\text{ml}$) before mixing with fresh autologous reactor lymphocytes. Control cultures included (a) unstimulated lymphocytes, (b) mitomycin C-treated unstimulated lymphocytes, (c) fresh lymphocyte reactor cells plus mitomycin C-treated autologous lymphocyte target cells, (d) PHA-incubated lymphocytes (72 hr), and (e) PHA-incubated lymphocytes treated with mitomycin C after the 72-hr incubation. The ^3H -thymidine uptake (2.0 μCi added four hours before harvesting) was greater at 72 hr than at 144 hr, the usual allogeneic peak reaction time. To eliminate the possibility that PHA itself made any contribution to the blast transformation, several tests were made. The supernatants of washed PHA-transformed cells were tested for stimulator activity. The stimulation cells were also incubated with PHA for only one hour, allowing for binding, and then tested for activity. In both cases, no stimulation of autologous lymphocytes occurred. Lytic sonication of the PHA-transformed cells destroyed their stimulating ability, whereas sonication of PHA itself had no effect on its stimulatory action. Although N-acetyl-D-galactosamine (NAGAL, 10 mg/ml) competes with PHA for lymphocyte membrane sites, incubation of the reactor lymphocytes with NAGAL did not diminish their response to PHA-transformed autologous lymphocytes. These results suggest the presence of autorecognition determinants on membranes of transformed lymphocytes.

5707 LEUKOCYTE MIGRATION INHIBITORY FACTOR (LMIF) INDUCED BY CONCAVALIN A: STANDARDIZED MICROASSAY FOR PRODUCTION *IN VITRO*. (Eng.) Gorski, A. J. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Dupont, B.; Hansen, J. A.; Good, R. A. *Proc. Natl. Acad. Sci. USA* 72(8):3197-3200; 1975.

An improved microculture system was developed for assessing the ability of lymphocytes to secrete leukocyte migration inhibitory factor (LMIF) in response to the nonspecific mitogen concanavalin A (Con A). The method was used to compare LMIF production by normal human lymphocytes with LMIF production by lymphocytes from patients with malignant lymphomas. The

human lymphocytes were isolated from heparinized blood by gradient centrifugation on Ficoll-Isopaque. The cells were set up as cultures in the presence of a final concentration of Con A of 4 $\mu\text{g/ml}$. Supernates of the cultures were used as the sources of LMIF produced. Cells used for migration were granulocytes obtained from whole blood and purified by removal of lymphocytes. The test consisted of measurement of inhibiting effect of supernates of LMIF-producing lymphocytes on the growth of cultures of granulocytes in agarose wells. Studies were performed on lymphocytes obtained from 29 normal blood donors and from 22 patients with Hodgkin's disease and with non-Hodgkin's malignant lymphoma. It was found that normal lymphocytes stimulated with Con A secreted a significant amount of LMIF compared to lymphocytes from unstimulated cultures. Further, the lymphocytes from most of the patients with lymphoproliferative malignancies failed to show an increase in LMIF production under the same conditions. In fact, some of the patients appeared to produce migration stimulation factor. To test whether the production of LMIF in microculture might be dissociable from lymphocyte transformation, the effect of radiation on the 2 phenomena was determined. Lymphocytes irradiated with a range of doses were tested for LMIF production in the presence and absence of Con A and for transformation by Con A as measured by uptake of ^{14}C thymidine. The results showed that LMIF production was unaffected by irradiation of the lymphocytes while the proliferative cell response was abolished. This finding that mitogen-induced LMIF production can be evaluated independent of proliferative capacity may be of value in analyzing immune responses at the cellular level in patients with different forms of immune deficiency.

5708 ENHANCEMENT OF TUMOR GROWTH IN ALLOGENEIC MICE FOLLOWING IMPAIRMENT OF MACROPHAGE FUNCTION. (Eng.) Isa, A. M. (Meharry Medical Coll., Nashville, Tenn. 37208); Sanders, B. R. *Transplantation* 20(4):296-302; 1975.

Because macrophages appear to be involved in tumor immunity, it was of interest to examine the effects of antimacrophage serum (AMS) on tumor growth. The AMS was prepared by injecting rabbits with macrophages obtained from the peritoneal cavities of thioglycollate-stimulated mice. The tumor used was the transplantable teratoma 402AX, derived from strain 129/J mice. It was tested for growth in male and female BALB/c and syngeneic mice. When the test mice were injected ip with 0.25 ml of a 20% dilution of AMS, the growth of the tumor at the site of injection was enhanced compared to that of controls in which normal rabbit serum (NRS) was administered instead of AMS. The enhancement was revealed by shorter times of appearance of the tumor and shorter times of death of the host. The tumor grew faster and killed the host sooner in the AMS-treated male mice than in similarly treated female mice, indicating a hormonal influence. Further, tumor growth was slightly slower in allogeneic hosts than in syngeneic animals. These results indicated that enhancement was due to impaired macrophage function and that the macrophage

plays a significant role in resistance to this particular tumor. To determine whether the AMS affected the antibody-producing immune system, tests were made by fluorescence methods for presence of IgM, IgA, IgG₁, IgG_{2a}, or IgG_{ab} classes of antitumor antibodies on tumor cell surfaces of AMS-treated mice bearing the tumor. The finding of the presence of all classes of antitumor antibodies on tumor cells of these mice, as well as on tumor cells of control mice treated with NRS, showed that humoral response to the tumor was not suppressed by growth of the tumor and that the humoral response was independent of macrophage function. These bound antibodies did not, apparently, prevent tumor cells from multiplying and killing the host. Further, they were not cytotoxic to the target cells in the presence of rabbit or guinea pig complement. Thus, it is clear that although the teratoma 402AX was immunogenic, protective immunity to the tumor was not mediated by the antibody.

5709 ISOLATION OF ANTI-MYELOMA MEMBRANE ANTIBODIES FROM RABBIT XENOANTISERA USING MEMBRANE IMMUNOADSORBENTS. (Eng.) Stanislawski, M. (Laboratoire de Chimie des Proteines, Inst. de Recherches Scientifiques sur le Cancer, C.N.R.S., 94800-Villejuif, France). *Immunochimistry* 12(8): 707-711; 1975.

Murine myeloma (MOPC 173, MOPC 104E, and RPC20) and tissue membranes were crosslinked with glutaraldehyde and used as immunoadsorbents for the isolation in quantitative yield of anti-myeloma membrane antibodies from rabbit xenoantisera. Contaminating anti-plasma protein and irrelevant tissue, antibodies were first removed with plasma and liver adsorbents and the remaining unadsorbed anti-myeloma antibodies were isolated using a myeloma microsome membrane immunoadsorbent. The isolated antibodies were found pure by immunochemical criteria and retained their precipitating activity against myeloma and normal lymphoid cell microsome membranes. The use of adsorbents for the removal of undesired antibodies provides at the same time a convenient method for their quantitation.

5710 TUMOR-ASSOCIATED AND EMBRYONIC ANTIGENS IN SOLUBLE FRACTIONS OF A CHEMICALLY-INDUCED RAT COLON CARCINOMA. (Eng.) Steele, G., Jr. (Wallenberg Lab., Univ. Lund, Lund, Sweden); Sjogren, H. O.; Price, M. R. *Int. J. Cancer* 16(1):33-51; 1975.

Soluble intracytoplasmic protein fractions and solubilized tumor membrane preparations produced by 3 M KCl or papain treatment were isolated from a 1,2-dimethylhydrazine-HCl (DMH)-induced rat colon carcinoma, DMH-BU 1. Solubilized preparations were fractionated by DEAE cellulose and Sephadex G200 column chromatography. Crude extracts and fractionated materials were tested for their ability to inhibit the cytotoxicity of lymph node cells (LNC) from Wistar/Furth rats bearing isografts of an *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (NG)-induced colon carcinoma, NG-W1. Crude

extracts and all but one of the fractions possessed common rat colon carcinoma-associated antigens. None of the soluble preparations altered the cytotoxicity of LNC immune to polyoma-virus-induced sarcoma on polyoma target cells. Crude extracts and fractions were tested for their ability to inhibit the *in vitro* cytotoxicity of LNC harvested from multiparous Wistar/Furth females on rat fetal lung and fetal colon target cells. In blocking assays performed by incubating the soluble preparations with LNC on the target cells for the duration of the test, crude extracts and seven of the 11 fractions significantly inhibited LNC cytotoxicity on rat fetal lung target cells. It is postulated that these fractions contain embryonic antigen (EA). Three of these seven fractions were tested for their ability to block at the target-cell level and were found negative. However, upon adding to the fractions either FKE₁₀₀ (presumptive fetal-kidney-specific antibody) or FGE₁₀₀ (presumptive fetal-gut-specific antibody), blocking of LNC-mediated cytotoxicity was demonstrated at the target-cell level. Neither FKE₁₀₀ nor FGE₁₀₀ alone blocked when tested at the target-cell level. Complexes which blocked the cytotoxicity of LNC from multiparous females on fetal colon target cells did not alter the cytotoxicity of polyoma sarcoma-immune LNC on sarcoma target cells. A single fraction, No. 19, was incubated with FWE₁₀₀ (fetal widespread₁₀₀, presumptive fetal kidney, fetal heart and fetal-lung-specific antibody) in an attempt to form antigen-antibody complexes with most of the widespread EA. It is postulated that fraction No. 19 contains both widespread EA and gut-specific EA.

5711 DYNAMICS OF IMMUNE RESPONSE TO TUMOR ASSOCIATED ANTIGENS. (Eng.) Herberman, R. B. (Nat'l. Cancer Inst., Bethesda, Md.); Ting, C. C.; Holden, H. T.; Glaser, M.; Lavrin, D. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 258-263.

An investigation has been made into the intensities of the humoral and cell-mediated immune response of hosts harboring either progressive or regressive tumors. Three systems were used: (i) regressive tumors were induced in W/Fu rats by the sc inoculation of 10⁸ syngeneic (C58NT)D tumor cells, and progressive tumors by the inoculation of larger numbers of cells; (ii) regressive tumors have been induced by the sc inoculation of 5x10⁶ FBL-3 cells into syngeneic C57BL/6 mice, and progressive tumors by the ip administration of the cells; (iii) regressive primary tumors were induced by the im inoculation of C57BL/6 mice with certain stocks of murine sarcoma virus, and progressive tumors by the similar inoculation of certain other stocks of the virus. The antibody responses tended to be biphasic in hosts with regressive tumors, and the highest titers of soluble antibodies were usually found long after the disappearance of the tumor. Hosts with progressive tumors also often developed high levels of antibody.

The kinetics of cell-mediated cytotoxicity as measured by the ⁵¹Cr release assay were found to be similar in both the (C58NT)D and murine sarcoma virus systems, with a sharp rise and abrupt fall in reactivity early after inoculation. The same kinetic pattern was seen in hosts of either regressive or progressive neoplasms, but higher levels of response were usually found to be associated with regression. In the FBL-3 system, the pattern was different. A biphasic response of cell-mediated toxicity as measured by ¹²⁵I-iododeoxyuridine release was associated with regression: hosts to progressive tumors developed only very low levels of reactivity. Although *in vitro* assays of cell-mediated cytotoxicity do not completely parallel *in vivo* events, it may be possible by further analysis to relate these phenomena more closely.

5712 EVIDENCE FOR TUMOR-SPECIFIC ANTIGENS IN FILTERED TISSUE CULTURE MEDIA FROM HUMAN CANCER CELLS. (Eng.) Hickok, D. F. (Abbott-Northwestern Hosp., Minneapolis, Minn. 55407); Miller, L. *In vitro* 10(3/4):157-166; 1974.

A study was undertaken to determine whether or not tumor-specific antigen is present in the filtered medium taken from tissue cultures of human tumor cells. The tissue culture medium taken from seven-day-old cultures of cells taken from patients with cancer of the colon, lung, breast, bladder, or melanoma was filtered; and the filtrate, tissue culture tumor antigen (TCTA), was used to activate autologous lymphocytes. The activated lymphocytes inhibited the growth of autologous human cancer cells *in vitro*, but not the growth of normal autologous cells, allogeneic tumor cells, or xenogeneic tumor cells. Autologous serum blocked activation of the lymphocytes. Further, autologous serum, when incubated with autologous tumor cells, prevented the inhibition of tumor cell growth by activated lymphocytes. Marked specificity was noted, suggesting that these reactions may be of value in isolating human cancer antigens. Thus, TCTA may be a source of soluble tumor-specific antigens.

5713 DEMONSTRATION OF A TUMOR-ASSOCIATED SURFACE ANTIGEN IN MAREK'S DISEASE. (Eng.) Witter, R. L. (U.S. Dept. of Agriculture, ARS, Regional Poultry Res. Lab., 3606 East Mount Hope, East Lansing, Mich. 48823); Stephens, E. A.; Sharma, J. M.; Nazerian, K. *J. Immunol.* 115(1):177-183; 1975.

Evidence is presented for the presence of a Marek's disease (MD) tumor-associated surface antigen (MATSA) which is detectable on three classes of MD tumor cells. The three classes were represented by MD lymphoma cells, cultured cells of the MSB-1 lymphoblastoid line (developed in Japan), and JMV lymphoblastic leukemia cells (developed by rapid passage of a MD lymphoma which was originally induced by JM strain of MD virus). The antisera for the tests included chicken sera against JMV cells and rabbit sera against MSB-1 cells. The technique used was indirect membrane immunofluorescent stain-

ing of suspended viable cells. Titers of antisera were based on per cent cells found to be positive by membrane fluorescence. The surface antigen was not detected on normal chicken lymphocytes, on RPL-16 tumor cells (avian RNA virus-transformed cells), or MD virus (MDV)-infected fibroblasts that were positive for viral membrane antigen. Furthermore, the surface antigen appeared unrelated to embryonic or histocompatibility antigens. The MATSA's present on JMV, MSB-1 and MD lymphoma cells were related but were not identical. This was demonstrated by results of antiserum titration, absorption experiments with cells of the different lines, and blocking tests in which the ability of anti-MATSA serum to reduce the membrane reactivity of rabbit anti-MATSA for JMV or MSB-1 cells (and vice versa) was determined. The frequency of MATSA-positive cells in MDV-induced lymphomas was very low and ranged from 2.3 to 27.3%; only 10 of 14 tumor preparations contained a significantly greater proportion of positive cells than was demonstrated by staining with normal serum. The significance of MATSA to MD tumor immunity was not clear, since MATSA antibodies were not detected in a variety of high titer chicken anti-MDV tumor antisera and thus may not be a normal consequence of MDV infection and tumor induction.

- 5714 MONOCLONAL IgM AS A TUMOR-SPECIFIC TRANSPLANTATION ANTIGEN. (Eng.) Talal, N. (Veterans Admin. Hosp., San Francisco, Calif.); Sugai, S.; Witz, I. *Transplant. Proc.* 7(1/Suppl. 1):505-507; 1975.

An idiotype on the surface of lymphoma 141 tumor cells (a malignant lymphoma secreting a monoclonal immunoglobulin M, IgM) was identified by indirect immunofluorescence and the ability of 141 IgM to confer protective immunity against this tumor was investigated. The intensity of the fluorescence diminished with the dilution of the anti-idiotypic serum. Specificity of this staining reaction was confirmed by two inhibition studies using purified IgMs from lymphoma 141 and from a BALB/c plasmacytoma (104E); 141 IgM inhibited the staining completely whereas 104E had no effect. In two additional specificity controls, anti-idiotypic serum prepared against another B/W monoclonal IgM (108) and against lymphoma 141 failed to show fluorescence against lymphoma 141 cells and B/W transplantable lymphoma, resp. Additional evidence for the presence of idiotype determinants on lymphoma 141 cells was provided by cytotoxicity studies using labeled tumor cells. Protection against lymphoma 141 by prior immunization with 141 IgM was demonstrated in six-month-old male B/W mice grafted with lymphoma cells. Three of the five immunized mice showed tumor regression by day 35; one was sacrificed for cytotoxic studies and two showed a gradual growth of tumor and died two and three months later. In a second experiment investigating protective immunity, all two-month-old mice immunized with IgM survived past day 35 after tumor grafting (from a patient with Waldenström's macroglobulinemia); mice immunized with 104E IgM died before day 28. Sera from mice with regression tumors killed 7-20% of the labeled 141 lymphoma cells while sera from mice with progressive tumors

killed 1-5% of the tumor cells. These results demonstrate that humoral immunity was present in protector or regressor mice against the idiotypic determinant on the surface membranes of lymphoma 141. An additional experiment suggests that this immunity is present in the spleen of regressor and protected mice.

- 5715 STRUCTURAL SIMILARITIES BETWEEN A PRODUCT OF THE T/t-LOCUS ISOLATED FROM SPERM AND TERATOMA CELLS, AND H-2 ANTIGENS ISOLATED FROM SPLEEN CELLS. (Eng.) Vitetta, E. S. (Univ. Texas Southwestern Medical Sch., Dallas, Tex.); Artzt, K.; Berrett, D.; Boyse, E. A.; Jacob, F. *Proc. Natl. Acad. Sci. USA* 72(8):3215-3219; 1975.

To compare the structure of F9 antigen, which is expressed by primitive teratocarcinoma cells and sperm of mice, with that of serologically distinct H-2 antigen, as expressed by mouse spleen cells, experiments were carried out in which teratoma cell sperm, and spleen cells were radiolabeled, lysates of the radiolabeled cells were precipitated with F9- and H-2-specific hyperimmune sera, and the different immunoprecipitates were characterized by SDS/polyacrylamide gel electrophoresis. ^{125}I and ^3H -leucine were used for the labeling and Nonidet P40 for the lysing of the different cell preparations. Ig was removed from the spleen lysates by sandwich precipitation using rabbit anti mouse Ig and goat anti rabbit Ig. Ig-depleted lysates from spleen cells were each divided into four aliquots and treated with optimal amounts of anti F9 serum (prepared in syngeneic 129/Sv mice), anti H-2^a serum (A.BY anti ASL anti H-2^b serum (B6.H-2^k anti EL4), or normal mouse serum. The results of the immunoprecipitation studies demonstrated the presence of F9 antigen on both the F9 teratoma cells and sperm but not on spleen cells and, conversely, the presence of the H-2 antigen on spleen cells but not on F9 teratoma cells or sperm. The electrophoresis studies revealed the identical molecular weights and subunit structures of F9 and H-2 antigens, including the presence of a B2-microglobulin subunit. Under reducing conditions of treatment with mercaptoethanol, three peaks of radioactivity were found in all immunoprecipitate preparations having molecular weights of 44,000, 22,000, and 12,000-14,000 daltons, resp. While the major component of 44,000 was considered to represent a monomer it was not known whether the 22,000 dalton unit was derived from the monomer. The 12,000-14,000 dalton unit was taken to be the B2-microglobulin, not derived from the monomer. These findings suggest that there is a structural homology between F9 and H-2 antigens and that the genes in question may arise from a primitive gene concerned with cellular recognition.

- 5716 COMPARISON OF LUNG CANCER ANTIGENS. (Eng.) Hollinshead, A. C. (George Washington Univ. Medical Center, Washington D.C.); Sega, E.; Stewart, T. H. M.; Ricci, C.; Mineo, T. C. *Tumori* 61(2):125-128; 1975.

The relation between the soluble membrane antigens of human malignant lung cells and normal human lung

cells was investigated. The proteins of human malignant lung cells were separated on polyacrylamide gel electrophoresis (PAGE) and their profiles (GWU antigens) and those of proteins from E.R. (Rome antigens) were analyzed. Rome antigens which appeared to be identified with lung carcinomas consisted of a saline extract of a pool of lung carcinoma tissue, repeatedly absorbed until no normal tissue components were detected in a sensitive double immunodiffusion, set up using a New Zealand white albino rabbit anti-lung cancer-specific antiserum. PAGE analysis of the Rome antigen revealed that some of the antigens from normal lung cell soluble membrane were at least partially removed. Protein bands N1, N5, N6, and N7 were almost entirely removed with only faint bands remaining stained with Coomassie Brilliant Blue. The area of the bands indicated by N2 showed a disruption of four polypeptide chains rather than the two, but the material was not removed by absorption. Normal protein bands N3 and N4 were present in the same concentrations as in unabsorbed preparations. Six protein bands were associated only with the tumor preparation; the second protein peak of the absorbed material (as separated by chromatography) contained the antigen which reacted with rabbit antiserum prepared against squamous carcinoma tissues. Two normal lung cell components (associated with N2 and N3) remained after absorption. Only two (T4 and T5) of the six tumor associated protein bands remained; T4 was present in both squamous cell and oat cell carcinoma of the lung. In six cancer patients, only the three with lung cancer gave positive responses when the Rome antigen was tested and compared to GWU antigens. A patient with mixed squamous and adenocarcinoma, and one with oat cell carcinoma gave positive delayed hypersensitivity skin tests to GWU and Rome antigens. A patient with undifferentiated large cell carcinoma reacted to the GWU, but not the Rome preparation. Thus, it appears that there are common antigens associated with some of the forms of transformed lung cells of human tumors.

5717 NERVOUS SYSTEM ANTIGEN-3 (NS-3), AN ANTIGENIC CELL SURFACE COMPONENT EXPRESSED ON NEUROBLASTOMA C1300. (Eng.) Schachner, M. (Harvard Medical Sch., Boston, Mass. 02115); Wortham, K. A. *Brain Res.* 99(1):201-208; 1975.

Neuroblastoma C1300, a transplantable mouse tumor of sympathetic nerve cells which displays reversible differentiated features in cell culture, was characterized with respect to the surface antigenic component (NS-3) of the solid tumor as grown *in vivo* in A/J female mice. Antisera to live, non-enzymatically-treated tumor cells were raised in rabbits by a series of inoculations. The antiserum from the first bleeding, having the most cytotoxic activity for C1300 and least for A/J thymocytes and lymph node cells, was used for further study. Two absorptions with particulate fractions from liver, spleen, kidney and thymus tissues of adult (C57BL/6J x C3H/HeJ)F₁ mice, followed by a single absorption with tissue homogenates of A/J mice yielded a product having cytotoxic activity for C1300, a glioblastoma, and 6-day-old retinal

cells, but none for A/J lymph node cells or thymocytes. By indirect immunofluorescence tests using fluoresceinated goat anti-rabbit Ig antibody, more than 95% of the viable C1300 cells showed fluorescence; more than 95% of the A/J lymph node cells or thymocytes did not. Analysis of the preabsorbed antiserum for shared antigenic specificities as revealed by test-absorbing with various tissues of A/J and C57BL/6J mice showed that, except for C1300, brain and retina, no tissues showed expression of crossreactivity of antigens. Kidney carried a small amount of the antigen, recognizable only after repeated absorptions with kidney tissue. Tumors of non-nervous systems were negative for NS-3 as exemplified by A/J sarcoma A1, A/J leukemia RADAI, C57BL/6J leukemia EL4, BALB/c ascites plasmacytoma MOPC 70A, A/J leukemia ASL1 and BALB/c ascites sarcoma Meth A. Tumors of putative glial origin were positive, however, as exemplified by glioma G26, glioblastoma G261, another glioblastoma, ependymoblastoma, and ependymoblastoma EPA. Two *in vivo*-grown teratocarcinomas OTT2466 and 70427 also expressed NS-3. NS-3 was not detectable by absorption procedures in mouse brain prior to the fourth postnatal day, after which the level increased to adult level on day 24. The fact that various neural cell types express NS-3 points to the possibilities that NS-3 is either one molecular species indiscriminately distributed among many cell types, or is composed of several molecular species, all of which must be recognized on the target cell for a cytotoxic effect of anti-NS-3 to be seen.

5718 ALLOANTIGEN EXPRESSION OF A RAT MOLONEY SARCOMA. (Eng.) Jones, J. M. (Dept. Immunopathology, Scripps Clinic and Res. Foundation, 476 Prospect St., La Jolla, Calif. 92037); Feldman, J. D. *J. Natl. Cancer Inst.* 55(4):995-999; 1975.

Cells of a brown Norway (BN) rat Moloney sarcoma (MST) were examined for Ag-B and non-Ag-B specificities and also for relation between alloantigen expression and *in vivo* growth. The MST adapted to tissue culture in minimal essential medium 10% fetal bovine serum, and the cultured cells produced tumors when injected sc into BN rats. Various rat strains were used in the study for preparing alloantibodies and antitumor antibodies with different specificities. These specificities were assured by appropriate absorption of the different antisera. The rat strains and their genetic types included LEW (B1B1), BN (B3B3), (BN x LEW)F₁(BNL) (B1B3), LEW x BNL backcross (B1B1, B1B3), BN x BNL backcross (B3B3, B1B3), BN.B2 (B2B2), WF (B2B2), and AUG (B5B5). Alloantigen expression of the MST cells was determined by binding experiments using ¹²⁵I-labeled antibody. It was found that MST cells failed to express certain BN alloantigen specificities and bound only about 30-50% the amount of labeled alloantibody bound by normal BN spleen cells. MST cells lacked antigen specificities shared by BN and WF rats, but expressed some of the antigen shared by BN and AUG rats. Further loss of alloantigens that occurred with prolonged *in vitro* culture was associated with reduced viru-

lence of MST cells for syngeneic hosts and with increased expression of tumor-associated antigens. The LEW rats, which were resistant to MST cells, may have rejected the tumor on the basis of factors other than Ag-B antigens. It was noted that, although qualitative changes in alloantigen expression were indicated by the studies, it was not determined whether qualitative changes in tumor-related antigens might also have occurred.

5719 ANTIGENIC AND ENZYMATIC CHANGES IN INFECTED AND TRANSFORMED HUMAN DIPLOID CELLS.

(Eng.) Rose, N. R. (Wayne State Univ. Sch. Medicine, 540 East Canfield, Detroit, Mich. 48201); Mili-sauskas, V.; Zeff, G. *Immunol. Commun.* 4(1):1-16; 1975.

Human diploid fibroblasts, WI-38, were infected with various agents, and the levels of lysosomal enzymes were determined by immunochemical quantitation. The agents used for infection included mumps virus (ABC strain, 5.6×10^7 or 6×10^3 plaque-forming units/ml for 3 or 14 days, respectively), *Mycoplasma orale* (112 colony-forming units (CFU/ml), *M. salivarium* (112 CFU/ml), *Acholeplasma laidlawii* (113 CFU/ml), and *Toxoplasma gondii* (3.2×10^5 or 5×10^4 organisms/ml for 24 hr or 3-12 days, respectively). Esterase levels were raised by mumps virus and *T. gondii* infection. The concentration of β -D-glucuronidase was greatly increased in cultures infected with *T. gondii* and decreased by mycoplasma infection. Two cultures transformed by simian virus 40 (SV40) showed reduced levels of esterase compared with untransformed FL amnion cultures. A second amnion culture and a culture of transformed Detroit 551 fibroblasts were unchanged. The levels of acid phosphatase were sharply reduced in 3 of the 4 SV40-transformed cultures tested. Because no depletion in esterase isoenzyme was observed in WI-38 cells infected with any agent, the drastic decrease in esterase previously seen in SV40-transformed WI-38 cells must be due to the transformation.

5720 α -FETOPROTEIN AND EARLY HISTOLOGICAL CHANGES OF HEPATIC TISSUE IN DAB-HEPATO-CARCINOGENESIS.

(Eng.) Onoe, T. (Sapporo Medical Coll., Sapporo, Japan); Kaneko, A.; Dempo, K.; Ogawa, K.; Minase, T. *Ann. NY Acad. Sci.* 259:168-180; 1975.

Hepatic changes in rats administered 3'-Me-dimethyl-aminoazobenzene (3'-Me-DAB) were studied with respect to histological morphology and the presence in hepatic cells of α -fetoprotein (AFP), glucose-6-phosphatase (G-6-Pase), and isozymes of aldolase, acid phosphatase, and nonspecific esterases. The initial histological change after commencement of azo-dye ingestion was degenerative alteration in the hepatocytes. For example, a marked decrease in the G-6-Pase activity was observed 1-3 wk after ingestion. Some of the degenerated hepatocytes disappeared from the periportal areas of the hepatic lobule, leaving the rest fallen into megalocytosis, and oval-shaped cells began to proliferate in the periportal areas after two weeks and occupied almost half of each lobule up to the fourth week. The oval cells decreased in numbers

after the fourth week. In tests for G-6-Pase in ov cells, it was found that some of them, with negative or very low G-6-Pase activity, showed characteristic of ductular cells, whereas others appeared to be of hepatocytic nature, showing intense G-6-Pase activity. Various transitional types were also observed. The period of appearance of AFP in the sera was practically coincident with that of proliferation of the oval cells and the small hepatocytes in the tissue. From this finding, it is suggested that the transitional cells and the immature small hepatocytes produce AFP and secrete it into the blood. When a fluorescent method was used for detection of AFP in hepatic cells of the carcinogen-treated rats, it was found that the AFP-producing cells were identical with the transitional cells or the small hepatocytes. The amount of serum AFP appeared to be roughly parallel to the number of fluorescent cells in the tissue, although the elevation of serum AFP was somewhat delayed compared with the appearance of oval-cell proliferation. The period of AFP appearance coincided with the period in which a deviation in isozyme pattern of aldolase, acid phosphatase, and nonspecific esterases toward patterns of fetal and neonatal types was observed. It is concluded that oval-cell proliferation and its differentiation to hepatocytes may play a principal role in the occurrence of fetal deviation in the function of hepatic tissue during early stages of carcinogenesis.

5721 IMMUNODEFICIENCY TO HEPATITIS B VIRUS INFECTION AND GENETIC SUSCEPTIBILITY TO DEVELOPMENT OF HEPATOCELLULAR CARCINOMA.

(Eng.) Simons, M. J. (WHO Immunology Res. and Training Centre, Univ. Singapore, Singapore); Yu, M.; Shanmugaratnam, K. *Ann. NY Acad. Sci.* 259:181-195; 1975.

The high frequency of hepatitis B antigen (HB_sAg) in hepatocellular carcinoma (HCC) patients has led to the hypothesis that immunoresponsiveness to hepatitis B virus (HBV) may be deficient in some patients, and that the immune response deficiency may have a genetic basis. Radioelectrocomplexing (REC), a radioimmunoassay in gel based on the principle of counterimmunoelectrophoresis (CIE), was used to identify four HBV immune status subgroups in 117 Chinese HCC patients and in normal Chinese male blood donors: (a) HB_sAg + ve/HB_sAb + ve; (b) HB_sAg + ve/HB_sAb -ve; (c) HB_sAg -ve/HB_sAb + ve; and (d) HB_sAg -ve/HB_sAb -ve. These subgroups comprised 2, 6, 70, and 22%, respectively, among blood donors, and 32, 19, 23, and 26%, respectively, among HCC patients. Although the HBV exposure rates in the two groups were similar (78% and 74%), the immune complex rates and HB_s antigenic rates were significantly higher in HCC patients (25.7% and 68.9%, respectively) than in the blood donors (7.7% and 10.3%, respectively). It is proposed that the failure of termination of HBV infection revealed by these high rates reflects an immunodeficiency state characterized by an inability to produce high-avidity HB_sAb. The immunodeficiency might have a primary genetic basis, or it might be secondary to the immunosuppressive effects of concurrent viral or parasitic infections.

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Dennis, A. J. (Biomed. Sci. Sect., Battelle's Columbus Lab., Ohio); Wilson, H. E. *Ann. N.Y. Acad. Sci.* 243:73-80; 1975.

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See also:

- * (Rev): 5401, 5410, 5411, 5412, 5413, 5414, 5415, 5416, 5417, 5418, 5419, 5420, 5428, 5447, 5448, 5449, 5450, 5451, 5452, 5456
- * (Chem): 5526, 5546, 5554, 5555, 5566, 5571
- * (Viral): 5610, 5613, 5621, 5623, 5637, 5651, 5657, 5658, 5663
- * (Path): 5796

- 5765 INVERTED PAPILLOMAS OF THE URINARY
BLADDER. (Eng.) DeMeester, L. J.
(Mayo Clinic, Rochester, Minn. 55901); Farrow,
G. M.; Utz, D. C. *Cancer* 36(2):505-513; 1975.

A study of 20 patients (15 men and five women, mean age 60 yr) with inverted papilloma of the urinary bladder and urethra revealed that the lesion is a true neoplasm, benign in its histologic morphology and clinical behavior. Anastomosing epithelial cords containing microcysts and covered by a relatively normal epithelium were present in all lesions; the cords appeared to derive their vascular supply from the external stroma rather than from an internal connective tissue core, as in the typical papilloma. The microcysts rarely displayed columnar cells or secretory activity of lining cells. All but three lesions showed evidence of proliferative cystitis, and in all but two a lymphocytic infiltrate was observed about the margins or base of the lesion. Cystoscopic examination showed that the lesions were located on the bladder trigone, often extending to the vesical neck; they apparently arose as a result of chronic proliferative cystitis. The most commonly associated symptoms were hematuria and obstruction. Only one patient had a recurrence after cystoscopic resection and electrofulguration of the tumor base. The lesion may be mistaken for a low-grade transitional cell carcinoma, although the histologic appearance and the subsequent behavior are distinctly different. The benign character of the inverted papilloma is evident in its lack of dysplasia.

- 5766 CALCIFYING EPITHELIAL ODONTOGENIC
TUMOR: A HISTOLOGIC, HISTOCHEMICAL,
FLUORESCENT, AND ULTRASTRUCTURAL STUDY. (Eng.)
Solomon, M. P. (State Univ.-Kings County Hosp.
Center, 451 Clarkson Ave., Brooklyn, N.Y. 11203);
Vuletin, J. C.; Pertschuk, L. P.; Gormley, M. B.;
Rosen, Y. *Oral Surg.* 40(4):522-530; 1975.

A calcifying epithelial odontogenic tumor occurring in a 35-yr-old Negro woman is presented. A firm, intraoral, expansile swelling was found in the body of the left mandible. The mucosa overlying the lesion was intact while the tumor extended from cuspid to the second molar and involved an edentulous zone. Radiographic examination revealed a trilobulated, lytic, expansile mass; the tumor and adjacent teeth were removed under general anesthesia, followed by an uneventful postoperative course. Gross pathology of the surgical specimen noted an unencapsulated, irregularly shaped tan-pink mass measuring 4.0 x 2.0 x 1.0 cm. Most of the tumor was composed of sheets of polyhedral cells in a fibrous stroma, with enclosed foci of acellular, amorphous, eosinophilic material. Electron microscopy revealed tumor cells displaying cytoplasmic membranes thrown into innumerable long interdigitating microvilli, many well-developed desmosomes, and abundant round and oval large mitochondria and polyribosomes. Ultrastructurally the eosinophilic material consisted of a flocculent substance resembling basement lamina material admixed with collagen fibrils. Although the tumor was found adjacent to the enamel

space of an impacted tooth, no relationship with reduced enamel epithelium was demonstrated.

- 5767 MALIGNANT CHANGE IN CHRONIC VARICOSE
ULCERATION. (Eng.) Liddell, K. (Royal
South Hants Hosp., Southampton, England). *Prac-
titioner* 215(1287):335-339; 1975.

Five case reports of malignant changes occurring in chronic venous ulcers are presented. A 73-yr-old man with a long history of varicose veins, intermittent varicose eczema, and ulcers presented a massive leg ulcer. Chronic gravitation changes were noted on both lower legs, and a biopsy confirmed suspicions of squamous cell carcinoma. Above knee amputation was successful; histology of the lesion showed pseudo-carcinomatous hyperplasia with areas of definite carcinoma. A 64-yr-old woman with a 35-yr history of varicose veins presented a small varicose ulcer with a granulated center. Wide excision of the ulcer, and removal of deep fascia and cortical surface of the tibia were successful, while histology confirmed the squamous cell carcinoma. A 64-yr-old man with a long history of varicose veins, chronic varicose ulceration, and ulcer tissue overgrowth was treated by through-knee amputation. An 82-yr-old man with a chronic varicose ulcer of hypertrophied center also had moderately differentiated squamous cell carcinoma. A 77-yr-old woman presenting chronic gravitational eczema and ulcer with a raised margin, diagnosed as multicentric basal cell carcinoma, was treated with excision and skin grafting. Common suspicious features of the five cases especially noted include: an ulcer enlargement preceeding squamous cell carcinomas, excessive growth of granulation tissue, and histories of varicose veins and/or thermal injury. Treatment variously involves local surgery and grafting, radiotherapy, or amputation.

- 5768 PRECENTRAL CEREBELLAR VEIN IN CYSTIC ASTRO-
CYTOMAS OF THE VERMIS. (Eng.) Hopkins,
L. N. (E. J. Meyer Memorial Hosp., 462 Grider St.,
Buffalo, N.Y. 14215); Bakay*, L. *J. Neurol. Neuro-
surg. Psychiatry* 38(8):816-818; 1975.

A characteristic angiographic deformity of the precentral cerebellar vein seen in three cases of cystic astrocytoma of the vermis in children is reported. In each case, the juvenile astrocytoma presented as a large cyst with mural nodule occupying the cerebellar vermis superiorly. The mural nodule lay in the area of the roof of the fourth ventricle superiorly, displacing the ventricle forward. The cyst occupied the superior vermis. In all three cases, the precentral cerebellar vein was displaced forward and upward; the terminal portion showed a hook-like deformity. There are two implications of this correlation between the characteristic displacement of the precentral cerebellar vein angiographically and the pathology seen at surgery: 1) in tumors of this type a reasonable estimate of the pathology can be made from the characteristic deformity of the precentral cerebellar vein; and 2) the deformity suggests that the origin of these tumors is in the region of

the anterior medullary vellum or linula of the cerebellum. The smooth forward displacement with terminal hook-like deformity seen in these three cases has not been observed in any but cystic astrocytomas of the superior cerebellar vermis and should serve as a helpful angiographic sign in the diagnosis of cerebellar vermis astrocytomas.

5769 THE PATHOLOGY OF INVASIVE BREAST CANCER: A SYLLABUS DERIVED FROM FINDINGS OF THE NATIONAL SURGICAL ADJUVANT BREAST PROJECT (PROTOCOL NO. 4). (Eng.) Fisher, E. R. (Shadyside Hosp. Inst. Pathology, 5230 Centre Ave., Pittsburgh, Pa. 15232); Gregorio, R. M.; Fisher, B. *Cancer* 36(1):1-85; 1975.

A study was performed to identify a clinical (7 parameters) and pathological (32 parameters) profile of invasive breast cancer with prognostic and therapeutic implications. One thousand women with invasive, operable mammary cancer were prospectively randomized; women with clinically negative axillae (647 women) were treated by either radical mastectomy (210), total mastectomy and irradiation (216), or total mastectomy only (221) and these women with clinically positive axillae (353) were subjected to either radical mastectomy (176) or total mastectomy and irradiation (177). Simple descriptive terminology was most practical, as well as inclusive, for classification of histologic types and demonstrated a high degree of reproducibility. The incidence of these types was: infiltrating ductal without special features (NOS), 52.6%; medullary, 6.25%; lobular invasive, 4.9%; mucinous, 2.4%; tubular, 1.2%; adenocystic, 0.4%; papillary, 0.3%; carcinosarcoma, 0.1%; Paget's disease, 2.3%; combinations with NOS, 28.0%; and combinations of the aforementioned without an NOS component, 1.6%. Oxyphilic or apocrine change and squamous metaplasia were regarded as features of tumor types rather than distinct entities and lesions comprised of small or multinucleated giant or basaloid cells were classified according to their basic growth pattern. The simplified method of histologic grading of breast cancer was based on the presence of tubule formation and nuclear grade. Seventy percent of the tumors were considered poorly differentiated (grade 3) and 2.5% were considered well differentiated (grade 1). A relatively large number of cancers exhibited some of the features of medullary cancer lacking either: 1) histologic circumscription, 2) marked lymphoid infiltrate, or 3) grade 1 nuclear forms (pure or, in part, tubular or adenocystic). Of 1123 examples of Paget's disease were associated with carcinoma of the underlying breast substance; only two of these were regarded as intraductal or noninvasive. Tumors 4.1 cm or larger were consistently associated with four or more positive axillary nodes, blood vessel and lymphatic invasion, and multicentric cancers. A severe cell reaction to the tumor suggested a high degree of malignancy rather than host resistance. Tumors containing calcium were significantly associated with glycogen, short-term treatment failure, and elastica. Noninvasive cancer in the vicinity of the primary tumor was associated with features of multicentricity and nodal metastases. Tumors of high-grade malignancy and proliferative fibrocystic disease of the breast were

more frequent among younger women (20-44 yr). Generally, nonwhite patients were younger, had longer duration of symptoms, and more likelihood for clinically positive axillae than Caucasian patients. A long interval (6 or more months) from the time of discovery of the tumor to surgical intervention was associated with larger tumors, clinically positive axillae, and skin involvement, but not treatment failure. The presence of clinically positive axillae, four or more nodal metastases, and tumors 4.1 cm or larger were associated with short-term treatment failure at all periods of observation. Lack of circumscription, lymphatic extension in the quadrants as well as tumors, age 20 to 54 yr and proliferative fibrocystic disease in the quadrants remote from the primary cancer were associated with short-term treatment failure at several, but not all observation intervals. Nipple involvement, absent sinus histiocytosis, skin involvement, perineural extension, marked tumor necrosis, presence of glycogen nuclear grade 1, and black race were found to be related to short-term treatment failure at only one observation period.

5770 PROLIFERATING ANGIOENDOTHELIOMATOSIS. (Eng.) Scott, P. W. B. (Armed Forces Inst. Pathol., Wash., D. C.); Silvers, D. N.; Helwig, E. B. *Arch. Pathol.* 99(6):323-326; 1975.

Biopsy specimens from three cases of proliferating angioendotheliomatosis were examined with the light and electron microscopes. The case histories of the patients; a 48-yr-old man, a 67-yr-old woman, and a 61-yr-old man; are presented. The electron microscope revealed atypical cells that were probably of endothelial origin: The predominant cell in the vessel lumen was oval-shaped and had an ovoid nucleus and cytoplasm that contained prominent ribosomes, scattered filaments, rough endoplasmic reticulum, and dilated mitochondria. In addition, basement membrane material was found on the extraluminal side of these cells. Pinocyte-like vesicles were found along the plasma membranes of the cells. Dark cells interspersed between the larger clear cells were interpreted as pyknotic endothelial cells. These studies suggest that the primary change in proliferating angioendotheliomatosis consists of vascular occlusion by cells of endothelial origin.

5771 SYNCHRONOUS CARCINOMA OF THE COLON AND RECTUM. (Eng.) Hancock, R. J. (Vancouver General Hosp., Vancouver, British Columbia, Canada). *Am. Surg.* 41(9):560-563; 1975.

The number, location, time of diagnosis, surgical treatment, association with polyps, and age distribution of synchronous carcinoma of the colon and rectum were investigated in 831 patients having a diagnosis of carcinoma of the colon and rectum over a 5-yr period (1968-1973). Of these 831 cases, 46 (26 male, 20 female) had synchronous carcinoma (5.5%), an incidence rate similar to that reported by other researchers. The 72% (33 of 46 cases) incidence of associated polyps is high compared to other series. Metachronous lesions were also recorded: 9 polyps (20%) and 5 carcinomas (11%). This

rate is also high; the incidence in the literature varies from 2-8%. Eight of the patients had other tumors as well: small bowel (2), ovary (3), and breast, thyroid and stomach (1 each). Only 50% of the patients in this series had the additional carcinoma in the same segment, leaving half of the patients with other lesions on opposite sides of the colon or with lesions separated by significant distances. Both situations probably contributed to the fact that only 25% were diagnosed preoperatively as having more than one primary lesion. A significant number were missed at operation (15%). About 50% of the patients in whom additional lesions were missed have died, many in less than 2 yr. It is suggested that more radical resection and extension of the use of subtotal colectomy and ileoproctostomy would have improved the results. Since patients with synchronous lesions have a higher incidence of metachronous lesions, particularly careful follow-up should be done. Six-month sigmoidoscopic and barium enemas are suggested. Serological tests for malignancy, recurrent or metachronous, may also be helpful.

5772 ENDODERMAL SINUS TUMOUR OF THE OVARY (A STUDY OF 27 CASES). (Eng.) Shrikhande, S. S. (Tata Memorial Hosp., Bombay, India); Sirsat, M. V. *Indian J. Cancer* 12(2):151-157; 1975.

A histopathological study of 27 cases of endometrial sinus tumor of the ovary is presented. While 59% of the cases occurred in the second decade of life, the age range was 11 mo to 31 yr. The majority of the cases complained of pain and swelling of the abdomen. The characteristic gross appearance of the tumor was variegated, with grayish-white areas alternating with reddish-brown hemorrhagic areas, and a nodular external surface. The characteristic histological appearance showed a loose, irregular meshwork with pleomorphic cells and vesicular or hyperchromatic nuclei of varying size. Tumor cells forming papillary projections, amorphous acidophilic material, and areas of hemorrhage and necrosis were also frequently noted. The tumor was found associated with other teratomatous elements in two cases and with dysgerminoma in one case. Histogenesis noted extremely undifferentiated tumor cells arising from the germ cells. A followup of 14 cases revealed that seven patients died within six months, while two died within one year of initial diagnosis. Four developed metastasis or recurrence; only one patient was alive and well after 1.5 yr. In one case, two types of tumors occurred in the two ovaries. Despite the varied treatment given, prognosis is very poor.

5773 PATHOLOGY OF VAGINAL AND CERVICAL ABNORMALITIES ASSOCIATED WITH PRENATAL EXPOSURE TO DIETHYLSTILBESTROL (DES). (Eng.) Robboy, S. J. (Clear-Cell Adenocarcinoma Registry, 275 Charles Street, Boston, Mass. 02114); Scully, R. E.; Herbst, A. L. *J. Reprod. Med.* 15(1):13-18; 1975.

The pathologic and cytologic features of vaginal and cervical abnormalities in young women exposed prenatally to diethylstilbestrol (DES) are described. Non-neoplastic alterations of the genital tract

related to DES exposure include vaginal adenosis, cervical erosion, and vaginal and cervical ridges. Adenosis has been found in about one-third of asymptomatic girls who have been examined in accordance with a history of prenatal DES exposure. The adenosis is usually characterized by a single layer of mucinous columnar cells resembling the lining cells of the endocervix or epithelial cells with eosinophilic or occasionally clear cytoplasm. Mucin pools are usually encountered and sometimes provide the only histological evidence of adenosis. Cervical erosions have been found in nearly all females exposed to DES *in utero*. In contrast to their frequent occurrence in vaginal adenosis, cells of tubal or endometrial type are rarely encountered, suggesting that the pathogenesis of cervical erosion and vaginal adenosis may differ. Transverse ridges have been found in about one-fifth of exposed patients. Similar to the cervical erosion, the surface of the cervical ridge is frequently lined by mucinous epithelium but rarely by tubal or endometrial epithelium. Vaginal ridges may be lined by either mucinous or endometrial-tubal type epithelium. Clear-cell adenocarcinoma may affect any region of the vagina. Approximately three-fourths of the tumors have a surface area of less than 12 cm², and of these the majority occur in the anterior wall. The most common cell types are clear cells that are filled with glycogen, and hobnail cells, that protrude into the lumens of the tubules and cysts. Metastases to pelvic lymph nodes have been demonstrated in 17% of stage I vaginal and 28% of stage I and stage II cervical carcinomas.

5774 MICROSCOPICAL CANCER OF THE STOMACH--A STUDY ON HISTOGENESIS OF GASTRIC CARCINOMA. (Eng.) Nagayo, T. (Aichi Cancer Center Res. Inst., Nagoya 464, Japan). *Int. J. Cancer* 16(1):52-60; 1975.

To elucidate the histogenesis of gastric cancer preceded by "chronic gastritis," 67 foci (58 cases) of cancer less than 5 mm in largest diameter were examined histologically. These cases were selected from 13,390 cases of stomach resection at Yokoyama Hospital, 1953-1973. Except in two cases, all minute cancerous foci were found unexpectedly in the mucosa of the antrum or of the angulus having peptic ulcer (42 cases) or gastric cancer (14 cases). They were more frequent in the lesser curvature than in other parts of the stomach. Histologically, 18 foci were found in an area close to the main lesion, while 40 were far from the lesion. Seven foci were detected in the mucosa adjacent to ulcer scars. In retrospective macroscopical examinations, 41 foci showed minimal erosion or tiny depressions on the affected mucosa, while in the other 26 no recognizable changes were observable. Histologically, the gastric mucosa outside the cancer lesions was more or less atrophic with or without intestinal metaplasia. All the minute cancers were found in the transitional zone between foveolar epithelium and pyloric glands corresponding to "generative cell layer" in autoradiographic studies. Poorly differentiated adenocarcinomas containing signet-ring cells occurred most often in combina-

tion with no or slight intestinal metaplasia of the mucosa, while well-differentiated adenocarcinomas always occurred in combination with a high grade of intestinal metaplasia. "Chronic gastritis" (atrophy of the pyloric glands leading to intestinal metaplasia) is considered the most essential change for the development of gastric cancer.

- 5775 CHARACTERIZATION OF THE MONONUCLEAR CELL INFILTRATE IN HUMAN MALIGNANT MELANOMA. (Eng.) Roubin, R. (Lab. recherches sur les tumeurs de la peau humaine, Fondation A. Rothschild, 29, rue Manin, 75019 Paris, France); Cesarini, J. -P.; Fridman, W. H.; Pavie-Fischer, J.; Peter, H. H. *Int. J. Cancer* 16(1):61-73; 1975.

The "blood atypical mononuclear cells" (AMC) were compared to the mononuclear cells of the skin infiltrate of melanoma-bearing patients. In the skin infiltrate of superficial spreading melanoma (SSM), nonphagocytosing mononuclear cells (NPMC) are a major cell component. The latter have morphological characteristics of mono- and lymphocytes. Twenty-five SSM, grade I-V, and blood from 13 healthy and six melanoma-bearing patients were used. The AMC were 5-20% of the nonadherent cell fraction from the controls and 6-9% of that fraction from melanoma-bearing patients. The NPMC and AMC were similar in size, and had in common ultrastructural features such as indented nuclei, dispersed organelles, rough endoplasmic reticulum profiles and surface microvilli. The two cell types were negative for non-specific esterase. They did not react for peroxidase at either the light or the electron microscopic levels, or adhere to glass. AMC did not form spontaneous E rosettes, had no surface IgG and no receptors for complement. They did form rosettes with SRBC coated with rabbit IgG (EAiGg). On frozen sections firm binding of EAiGg was seen on the skin infiltrate in 3 of 10 cases. Possibly NPMC react with tumor cells *in vivo*, in the same manner as do AMC *in vitro*.

- 5776 CARCINOMA HYPOPHARYNX--A REVIEW OF 150 CASES. (Eng.) Pandhi, S. C. (Dept. Otolaryngology, Post-graduate Inst. Medical Education and Res., Chandigarh, India); Mehra, Y. N.; Dutta, T. K.; Gupta, B. D. *Indian J. Cancer* 12(2):130-134; 1975.

One hundred and fifty cases of carcinoma of the laryngopharynx were analyzed. These included the pyriform sinus (71 cases), the postcricoid region (49 cases), and marginal zone (16 cases). The majority of pyriform sinus lesions presented during the 4th-6th decades. Postcricoid lesions were common in the 4th and 5th decades, yet patients ranged in age from 15-80 yr. Although pyriform sinus lesions were commoner in males, and the postcricoid lesions commoner in females, the sex ratio was 1:1.39. Hypopharyngeal carcinoma affected the agriculturists and laborers of poor and average socioeconomic status in 74.6% of the cases; positive histories of alcohol use, smoking, opium use, and coarse foods were noted. Dysphagia was the commonest presenting symptom (87.3-95.9%), followed by neck

swelling, neck pain, and hoarseness. Forty-one percent of the cases presented at Stage IV, 22.67% at Stage III, and 36.0% at Stage II. Nearly 66% of the pyriform sinus cases had lymph node involvement; half had ipsilateral mobile nodes, and others had bilateral mobile and/or fixed nodes. The cervical lymph nodes were involved in 40.8% of the postcricoid lesions, and the thyroid gland was infiltrated in 2.7%. Moderate or severe anemia was seen in 28% of the hypopharyngeal carcinoma cases, and in 25% of the postcricoid carcinoma cases. All tissues histopathologically examined were squamous cell carcinoma which was moderately-well differentiated in 86%. Despite recent advances in treatment, up to 20% of reported cases were untreatable due to generalized disease or advanced age. A curative dose of radiotherapy (5,000-5,500 rads) was given in 23%, a preoperative dose (3,500-4,000 rads) in 21.3%, and a palliative dose (2,500-3,000 rads) in 50.7% of the cases. Tracheostomy was done in 36.66%, and gastrotomy in 17.33%.

- 5777 INTRACYTOPLASMIC SEGMENT LONG SPACING FIBRILS IN CHONDROSARCOMA. (Eng.) Imura, S.-I. (Sch. Medicine, Kanazawa Univ., Kanazawa, Japan); Tanaka, S.; Takase, B. *J. Electron Microsc.* 24(2):87-95; 1975.

A secondary chondrosarcoma removed from the pelvis of a 32-yr-old woman was studied by electron microscopy. The cells in the peripheral area of the tumor were mostly spindle-shaped and occasionally had slender, irregular extensions of the cytoplasm. The nuclei were mostly oval, often showing invaginations in their membranes. Most cells had small mitochondria and a large Golgi apparatus consisting of lamellar membranes, vacuoles, smaller vesicles, and a poorly developed rough endoplasmic reticulum. The cell cytoplasm also contained secretory vacuoles near the Golgi apparatus. These vacuoles had dense granules measuring 50 A in diameter and fine filaments measuring 50 A in width. The cells in the central area of the tumor were large, round, or ovoid and had short cytoplasmic extensions. The nuclei were round or ovoid. Most of the mitochondria were large with attenuated cristae. The rough endoplasmic reticulum was poorly developed at the periphery of the cytoplasm. Golgi apparatus and secretory vacuoles were also seen. The most striking finding was cross-banded fibrils within the vacuoles near Golgi apparatus in the peripheral tumor cells. The fibrils were about 4,080-5,000 A long and 500-800 A wide, and were composed of two segments having 31-33 substriation. They had an axial period of about 2,500 A, and were characterized by fine asymmetrical banded structures. Other vacuoles contained fibrils 200-500 A wide without a discernible periodicity and dense granules. The extracellular matrix was composed of fine filaments associated with dense granules and fine fibrils. These cross-banded fibrils are essentially identical with previously described fibrils produced *in vitro*. Although the intracytoplasmic fibrillogenesis in this tumor does not represent a normal process of collagen fiber formation, the suggestion is made that tropocollagen molecules are synthesized in the polysome on the rough endoplasmic reticulum;

they then travel to the Golgi apparatus and aggregate in the manner characteristic of segment long spacing fibrils under appropriate conditions, including such pathological conditions as those associated with cartilaginous tumors.

- 5778 SEBACEOUS CARCINOMA. (Eng.) Salm, R.
(Royal Cornwall Hosp., Dept. Histopathology and Dermatology, Truro, Cornwall, U.K.);
Wright, G. E. *Beitr. Pathol.* 155(3):221-236; 1975.

Case histories of 11 sebaceous carcinomas are reported, and the findings are discussed together with those of previous studies. In the 11 new cases (four male, seven female, 45-80 yr), none of the tumors recurred or metastasized after excision. Two growth patterns were observed: basal-cell carcinomas with sebaceous differentiation, and pure sebaceous carcinomas. In the cases in which the duration was recorded, the history extended over many years. Seven of the 11 cases occurred on the face, two on the shoulder, and one each on the scalp and thigh. The literature review indicated that most sebaceous carcinomas occur on the face and scalp and less frequently on the trunk, limbs, scrotum, and vulva. The typical lesion is a solitary, nonulcerated, firm intradermal nodule or plaque, and most are clinically benign. The tumors often incorporate small cysts, which are caused by two different processes: Some are due to degeneration of tumor cells and sometimes contain albuminous fluid and cholesterol-crystal clefts; the second type is lined by a thin squamoid zone, and when these are numerous, the growth resembles a trichoepithelioma. Occasionally such cysts are completely filled with lamellated keratin, and when these are plentiful, the tumor resembles a keratotic basal-cell carcinoma. Histological diagnosis rests on the presence of the characteristic sebaceous tumor cells. If sebaceous differentiation is minimal, however, it may be overlooked; such tumors can thus be reported instead as basal-cell, squamous-cell, intraepidermal, or metastatic carcinomas. The lesions may also be misinterpreted as hypernephromatous deposits or as sweat-gland carcinomas or xanthomas. It is concluded that sebaceous carcinomas arise from field changes in the epidermis, in the skin appendages, or in both. They are essentially subtypes of basal-cell carcinomas.

- 5779 INCREASING OCCURRENCE OF TUMOUR CELL--
TUMOUR CELL EMERIPPOLEIS IN THE REGEN-
ERATING JB-1 ASCITES TUMOUR. (Eng.) Chemnitz, J.
(Dept. Anatomy, Univ. Odense, DK-5000 Odense,
Denmark); Skaaring, P.; Bichel, P. *Z. Krebsforsch.*
84(1):89-96; 1975.

Tumor cell--tumor cell emeripoleis was studied in the regenerating JB-1 ascites tumor by transmission electron microscopy, autoradiography, and light microscopy. The tumor is a hypotetraploid transplantable plasmacytoma that has been maintained syngeneically in inbred AKR/Aa mice by ip injection of 5×10^6 tumor cells every ninth or tenth day. The mice used in this study were inoculated ip with 2.5×10^6 tumor cells. Ten days after transplantation the ascites tumor was

aspirated. JB-1 tumors in recurrent growth were obtained by aspiration four hours (four mice) and 24 hr (eight mice) after the first aspiration. The aspirated cells were centrifuged, and the pellets were embedded in Araldite before semi-thin (0.5 μ m) and ultra-thin sections were cut. Twenty-four hours after aspiration, the tumor cells of four mice were flash labeled ip with [3 H]thymidine, and 20 min later a small sample of the tumor was taken. Semi-thin and ultra-thin sections were prepared for microscopy, and semi-thin sections were also treated for autoradiography. Light microscopy of sections from 24-hr cells revealed 4-8 cases of emeripoleis in 16,000 cells. Most cases were markedly alike, showing an outer cell with one large vacuole containing a smaller inner cell. Both cells had distinct nuclei with conspicuous nucleoli in a dense homogenous cytoplasm. Several cases differing from this typical appearance were observed such as: (a) inner cell in mitosis while the outer cell apparently was in interphase; (b) inner cell in the process of disintegration; and (c) outer cell containing one small and one large vacuole, the latter containing a cell which again contained a large clear vacuole. The fine structure of emeripoleis cells was examined in sections obtained from the autoradiography specimens. The nuclei were very much alike and in both cells there were microprojections extending into the vacuole, pinocytotic activity, numerous ribosomes and a few A-type virus-like particles in the granular endoplasmic reticulum. These results indicate that the cells are two separate cells, and that the phenomenon of emeripoleis comes into being by cytophagocytosis.

- 5780 THE 125 I THYROID SCAN: CLINICOPATHOLOGIC CORRELATION. (Eng.) Russell, C.
D. (Univ. Alabama Medical Center, Birmingham, Ala. 35294); Webber, M.; Waisman, J. *Int. J. Nucl. Med. Biol.* 2(3):129-134; 1975.

Over a 3 1/2-yr period during which 125 I was used as the routine agent for thyroid imaging at the UCLA Hospital and Clinics, 95 cases of thyroid disease in which a tissue diagnosis was obtained were reviewed. The photo scans were reviewed by one experienced observer and the surgical specimens were reviewed by an experienced pathologist; neither had knowledge of the clinical findings or the findings of the other. The pathological specimens included 31 adenomas, 29 nodular goiters, eight diffuse hyperplasias, 12 papillary carcinomas, seven follicular carcinomas, one medullary carcinoma, three intrathyroid cysts of undetermined etiology, one extrathyroid cyst of undetermined etiology, three thyroglossal duct cysts, two Hashimoto's thyroiditis, one subacute thyroiditis, and one normal thyroid. All but three abnormal photo scans fit one of five major patterns: diffuse hyperplasia, solitary nodule (hot, warm, or cold), or multiple nodules. A hot nodule showed greater activity than the remaining gland; a warm nodule showed the same activity; and a cold nodule showed less activity. There was good correlation between the scan appearance of diffuse hyperplasia and the pathologic diagnosis of diffuse hyperplasia; there were seven

correct classifications, one false positive, and one false negative. In contrast, the scan findings were of little value in separating the carcinomas from the nodular goiters or adenomas. This was true even in cases presenting as nontoxic solitary or multiple nodules with no clinical evidence of malignancy. The only criterion that showed a statistically significant difference between benign and malignant nontoxic nodules was the size of the gland; enlarged glands tended to be benign. It is concluded that ^{125}I , like ^{131}I , is of real but sharply limited value in separating benign from malignant thyroid disease.

- 5781 A CYTOGENETIC STUDY OF GONADOBLASTOMA TISSUE IN TWO CASES. (Eng.) Philip, J. (Dept. of Obstetrics and Gynecology, Rigshospitalet, Tagensvej 18, 2200 Copenhagen N, Denmark); Hansen, M. K.; Reintoft, I. *Acta Pathol. Microbiol. Scand.* [A] 83(5):559-567; 1975.

Cytogenetic investigation of two new cases of gonadoblastoma, in a phenotypic female and phenotypic male, is presented. An 18-yr-old female experienced slight virilization, primary amenorrhea, small breasts, an infantile uterus, and a single, moderately enlarged, indolent ovary. Elevated urinary excretion of pituitary gonadotropins was noted. The uterus and tubes were macroscopically and microscopically normal; however, the left ovary consisted of a smaller lobular tumor and a larger cystic tumor. Both ovaries were built up of tissue with collagen fibers, within which were arranged germ cells, granulosa-Sertoli cells, and Leydig cells. The histological diagnosis was gonadoblastoma with dysgerminoma and teratoma of the left ovary and fibrous streak with gonadoblastoma of the right ovary. A 25-year-old phenotypic male presented with aspermia, a low excretion of pituitary gonadotropins, and empty scrotum. Herniotomy and laparotomy followed by pathological diagnosis revealed a rudimentary uterus, a small macroscopic ovary, and somewhat lobular tumor tissue in the gonads. The histological diagnosis of the gonads was gonadoblastoma with seminoma. In both patients, a repeated laparotomy was performed for removal of the remainder of the gonads, following diagnosis. Successful cultures derived from such gonadoblastoma tissue revealed a modal chromosome number of 46 and the karyotype 46, XY with normal autosomes in both patients. It is expressed that the results obtained support the hypothesis that gonadoblastomas (gonocytoma III) originate from gonads that are dysgenetic testes.

- 5782 MULTIPLE PRIMARY LUNG CANCERS. (Eng.) Martini, N. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, N.Y. 10021); Melamed, M. R. *J. Thorac. Cardiovasc. Surg.* 70(4):606-612; 1975.

Twenty years of clinical experience with 50 patients having multiple separate primary carcinomas of the lung are summarized, and criteria for distinguishing such multiple primary lung cancers from intrapulmonary metastases are briefly presented. Of the

50 patients (38 men, 12 women) 18 had synchronous tumors and 32 had metachronous tumors, the intervals between diagnoses ranging from 4 mo - 16 yr. Two separate cancers were identified in 49 cases, and three cancers were identified in one patient. Histologic patterns in the two different carcinomas were the same in 31 patients, most commonly epidermoid. The tumors were located in different lungs in 33 patients, in separate lobes of the same lung in seven patients, and in separate segments of the same lobe in ten patients. Fifteen of 18 patients with synchronous carcinomas underwent thoracotomy and resection of the tumors; diagnosis of cancer in the three remaining patients was established at autopsy. In all 32 patients with metachronous cancers, the first tumor was managed surgically as was the second tumor in nearly 60% of the patients. Twelve patients were treated with radiation for the second tumor. Two or three separate carcinomas were accepted as primary in the lung in those cases where the tumors were of different histology, particularly when they were widely spaced in time and location. The most difficult cases were those tumors of similar histology appearing at the same time in the same lobe. Primary epidermoid carcinomas were identified by tracing their origin from carcinoma *in situ*. Other tumor types were accepted as primary only if it could be shown that there was no reasonable expectation of metastasis from one site to the other. Conserving lung tissue at the original operation is important in order to allow the patient who develops a second lung cancer to be treated by resection without undue jeopardy to his already limited pulmonary reserve.

- 5783 LIVER TUMORS AND ORAL CONTRACEPTIVES. (Eng.) Nissen, E. D. (1751 West Romneya Drive, Anaheim, Calif. 92801); Kent, D. R. *Obstet. Gynecol.* 46(4):460-467; 1975.

Three case histories are presented of women who had benign hepatocellular neoplasia after taking oral contraceptives of various types; another twenty such cases are reviewed. All three cases (one 22- and two 27-yr-old) complained of upper right quadrant abdominal pain. One patient who had had abdominal pain for 15 hr when he was seen in the emergency room in shock had a perforated necrotic tumor of the liver with massive bleeding. A diagnosis of hepatocellular adenoma was made. The other two patients underwent partial hepatectomy and were diagnosed as having focal nodular hyperplasia. None of the 23 reported cases had a history of liver disease, alcoholism, or ingestion of hepatotoxic drugs. Duration of oral contraceptive use varied from 6 mo to an indefinite number of years in 2 of 4 patients who died. Eleven patients had hemoperitoneum due to hemorrhagic necrosis of their liver tumors; four of these patients died after surgery. The right liver lobe was affected in 13 patients, in keeping with previously published views that focal nodular hyperplasia more frequently involves the right lobe. In the entire series, there was only one 5-yr survivor. Only eight patients have been followed longer than 1 yr. Because the first report was published in 1972 and other cases were recently

discovered in retrospect, evaluation of results is difficult. Nevertheless, it is suggested that since progestogens are enzyme inducers it is possible that they accelerate oncogenesis by increasing toxic metabolites which cannot be excreted due to the cholestatic effect of the estrogens. Vascular changes and the hypercoagulation state of oral contraceptive users may act synergistically to produce hemorrhagic necrosis and tumor rupture.

- 5784 BRONCHIAL CARCINOID TUMORS. (Eng.) Salyer, D. C. (The Johns Hopkins Hosp., Baltimore, Md. 21205); Salyer, W. R.; Eggleston, J. C. *Cancer* 36(4):1522-1537; 1975.

Twenty-eight pulmonary carcinoid tumors were reviewed histologically and clinically. Hematoxylin-and-eosin-stained sections were utilized, as well as special stains, including the argyrophil and argentaffin reactions. The 22 tumors located centrally, at the level of primary or segmental bronchi, exhibited striking cellular uniformity. Their most common growth pattern was solid sheets of cells in a mosaic arrangement. Mitoses were absent or very rare. Five of the six peripheral tumors were characterized by a disorganized growth pattern, with crowding and lack of cell orientation. Mitoses were rare. One large peripheral tumor appeared much more aggressive histologically with up to seven mitoses per five high-power fields. This tumor was designated an atypical carcinoid. The gross and microscopic findings indicate that central and peripheral carcinoids may arise from Kulchitsky cell precursors in the mucous glands and peripheral bronchial epithelium, respectively. The overall mortality rate for this series is 7.4% (of 26 patients).

- 5785 HEPATOMA ASSOCIATED WITH ANABOLIC STEROID THERAPY. (Eng.) Holder, L. E. (Union Memorial Hosp., Baltimore, Md.); Gnarra, D. J.; Lampkin, B. C.; Nishiyama, H.; Perkins, P. *Am. J. Roentgenol. Radium. Ther. Nucl. Med.* 124(4):638-642; 1975.

An 11-yr-old boy with Franconi's anemia who developed a hepatoma after 50 mo of therapy with anabolic steroids (e.g., fluoxymesterone and oxymetholone) is reported. Initial static and dynamic liver scintigraphy with ^{99m}Tc sulfur colloid showed hepatocellular disease which was manifested by a diffusely enlarged heterogeneous liver and by increased spleen and bone marrow uptake. A cold focal defect present in the static scintigram was dynamically avascular, and this suggested either an abscess or a fibrotic pseudotumor. The differential diagnosis was complicated by the fact that the patient was febrile, had acute hepatitis, and may have had subclinical hepatitis previously. Repeat scintiscans four months later revealed a well-defined lesion, which continued to be avascular. A well-differentiated hepatoma measuring 4 x 3.5 cm was found at autopsy. Nuclear radiologists should be aware of the association between anabolic steroid therapy and hepatocellular carcinoma. Liver scintigraphy provides the prime mechanism for

discovering focal lesions in patients in whom other liver function studies are often abnormal secondary to hepatitis, cirrhosis, or drug-induced hepatocellular toxicity. As this case shows, avascularity on the dynamic study cannot rule out hepatoma from the list of differential diagnostic possibilities.

- 5786 STUDIES OF PARENTS OF CHILDREN WITH ACUTE LEUKEMIA. (Eng.) Hann, H. W. L. (Inst. for Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, Pa. 19111); London, W. T.; Sutnick, A. I.; Blumberg, B. S.; Lustbader, E.; Carim, H. M.; Evans, A. E.; Kay, H. E. M.; MacLennan, I. C. M. *J. Natl. Cancer Inst.* 54(6):1299-1305; 1975.

In a case-control study, 70 mothers and 24 fathers of children with acute leukemia (AL) were compared with 70 mothers and 24 fathers of normal children. Thirty-five blood factors of parents of children with AL were tested and compared with parents of normal children. The tests included complete blood count, liver function, antistreptolysin titer, Kell antigen, WBC differential, antinuclear antibody, rheumatoid factor, hepatitis B antigen and anti-hepatitis B detection, Epstein-Barr virus viral capsid antigen, immunoglobulin (IgG, IgA, IgM, IgD) detection, antithyroid antibody, and skin tests (tuberculin and mumps antigen). Three significant differences ($P < 0.05$) were found when the 35 factors were compared among the mother pairs, and one difference was found among the father pairs. Mothers of children with AL, though alike in most respects to their matched (age and parity) controls, had a significantly lower number of monocytes than their controls. This is a new observation. In the group from Children's Hospital of Philadelphia, IgG was significantly elevated in 47 mothers of children with AL; in 23 mothers of AL children from the Royal Marsden Hospital, London, IgG was less than in controls. The fathers and mothers had higher levels of basophils. These findings direct attention to the immune systems, particularly the mononuclear cells, of the parents of children with AL, as a focus for further studies on the etiology and pathogenesis of childhood leukemia.

- 5787 PATHO-ANATOMICAL FEATURES OF SO-CALLED Ph^1 -- CHRONIC MYELOID LEUKEMIA. (Eng.) Schwarze, E. W. (Pathologisches Institut der Universität Kiel, D-2300 Kiel 1, Hospitalstr. 42, West Germany); Schwalbe, P.; Klein, U. E. *Virchows Arch. [Pathol. Anat.]* 367(2):137-148; 1975.

Chronic myeloid leukemia (CML) without the Philadelphia chromosome (Ph^1 -CML) is described and distinguished from CML with the Philadelphia chromosome (Ph^1 +CML). Four men, aged 53-83 yr, were studied. Before therapy, the leukocyte counts of all four patients were less than 50,000 cells/ μl , all were anemic on admission (4.3×10^6 to 1.2×10^6 erythrocytes/ μl), had low thrombocyte counts, lacked the Ph^1 chromosome, and displayed hepatosplenomegaly and enlarged lymph nodes. At autopsy, histological features of the bone marrow included severe myeloproliferation, reduced

numbers of erythrocytopoietic cells, greatly diminished megakaryocytopoietic cells, and a diffuse increase in the number of reticular fibers. All patients demonstrated hepatomegaly; in addition, there was strong leukemic infiltration of the periportal spaces, slight-to-moderate infiltration of the sinusoids, and collapsed peripheral parts of the liver acini. Spleen weights ranged from 400-2125 g, accompanied by a generalized enlargement of the lymph nodes. Leukemic infiltration was noted in the tonsils, medullary and paracortical pulp, the capsule, trabeculae, and paracortical tissue. Additional leukemic infiltration was found in the bronchial walls and peribronchium, the renal cortex, the mucosa of the stomach, small bowel, and colon, plus predominantly small leukemic infiltrates in various other organs. The characteristic morphological differences noted between Ph¹-CML and Ph¹+CML are the distribution of leukemic infiltrates in the liver and other organs, and lymph node infiltration.

5788 VIRUS-BEARING PLASMA CELLS IN PERIPHERAL BLOOD OF A PATIENT WITH 'HAIRY CELL' LEUKEMIA. (Eng.) Pedio, G. (Institut für Pathologische Anatomie, Kantonsspital, CH-8006 Zurich, Switzerland); Ruttner*, J. R.; Spycher, M. A.; Gut, D. *Acta Haematol. (Basel)* 54(5):297-305; 1975.

The peripheral blood of a patient with 'hairy cell' leukemia was studied using electron microscopy. The bone marrow of the 60-yr-old woman was hypocellular and contained slightly decreased number of megakaryocytes and about 12% classical 'hairy cells'. In addition, the lymphoid cells were atypical (5-7 µm diameter, showing small cytoplasmic protrusions) and numerous pathological plasma cells were observed. Osmiophilic granular material coated the cell surface of 'hairy cells' and lymphoid cells but not the plasmalemma of the plasma cells. The most important features of the plasma cells were cytoplasmic protrusions and masses of oncogenic virus A particles in their endoplasmic reticular cisternae. The presence of these particles suggests a viral nature for this disease. On the other hand, these viruses might represent 'passenger' viruses or nonspecific cell reactions.

5789 A MURINE MODEL FOR CENTRAL NERVOUS SYSTEM LEUKEMIA AND ITS POSSIBLE RELEVANCE TO HUMAN LEUKEMIA. (Eng.) Lynch, R. G. (Washington Univ. Sch. Medicine, St. Louis, Mo. 63110); Medoff, G.; Valeriote, F. *J. Natl. Cancer Inst.* 55(3):611-617; 1975.

The occurrence of CNS leukemia in female AKR mice was studied after therapy for a transplanted leukemia. The mice either received 0.5 mg amphotericin B (AmB) three days after iv inoculation of 10⁶ leukemia cells followed by 0.2 mg 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) on day 4, or AmB was administered daily for four days after leukemia cells were given and BCNU administered on day 4. Both agents were injected ip. Forty percent of leukemic mice treated with AmB and BCNU survived for 21 days or longer. In contrast, mice treated

with AmB or BCNU alone died within eight days of injection of leukemia cells as did untreated controls. Minimal to moderate infiltration of the CNS by leukemic cells was noted in 20 of the 34 short-term survivors. Twenty of the 37 long-term survivors developed paralysis, the severity of which was correlated with the extent of leukemic infiltration of the CNS. All 18 mice with paralysis of two or more extremities had a thick mantle of leukemia cells in the meninges with compression of the cerebral hemispheres; 10 of the 18 had extension of leukemia cells from the CNS along cranial and spinal nerves. Twelve of the 20 paralyzed long-term survivors had their leukemia restricted to the CNS, while eight animals had both CNS and systemic disease. Systemic disease in these animals was generally less extensive than in short-term survivors and the pattern of organ involvement differed in that spleen and lymph node involvement was rare. Unlike the short-term survivors, few long-term survivors had leukemia cells in the cranial bone marrow. Both long-term survivors with minimal paralysis (one limb) were without either CNS or systemic leukemia involvement. None of the 17 nonparalyzed animals had systemic disease, but one had advanced CNS leukemia and two had minimum CNS involvement. The occurrence patterns and histopathologic features of the CNS leukemia in the long-term survivors were strikingly similar to those observed in humans with acute lymphoblastic leukemia. On the basis of this work and earlier studies, vigorous prophylactic therapy to prevent clinical CNS leukemia and systemic spread in humans appears justified.

5790 ANTICONVULSANT-INDUCED LYMPHOMA. (Eng.) Fried, M. P. (517 South Euclid Ave., St. Louis, Mo. 63110); Sunwoo, Y. *Laryngoscope* 85(10):1770-1781; 1975.

A case history of anticonvulsant-induced pseudo-lymphoma is presented to illustrate the difficulty of distinguishing between true lymphoma and a benign clinical entity with the histologic characteristics of lymphoma. A patient (male, 43 yr) on diphenylhydantoin for control of alcohol withdrawal seizures developed bilateral true vocal cord paralysis and cervical adenopathy. Thorough evaluation of the cause of the vocal cord paralysis was undertaken, but no etiology was found. Microscopically, the cervical lymph node was infiltrated with pleomorphic atypical reticulum cells, lymphocytes and plasma cells. Many of the reticulum cells were large, with pleomorphic nuclei and mitotic figures. Binucleated cells resembling Reed-Sternberg cells were seen but no typical Reed-Sternberg cells were found. Invasion of the capsule by lymphocytic and reticulum cells was seen. Upon withdrawal of treatment, the lymphadenopathy regressed, suggesting a diphenylhydantoin-induced process. Seventeen months after the onset of cord paralysis, the patient was readmitted with stridor, cervical adenopathy and fluid retention. Another cervical lymph node biopsy revealed a cellular node with proliferation extending to the subcapsular sinuses and outside the node, which was composed mainly of mature lymphocytes. A diagnosis of malignant lymphoma with

plasmocytic differentiation was made. No malignancy developed, however, during an observation period of more than two yr after the appearance of the cervical adenopathy and the diagnosis was changed to hydantoin-induced pseudolymphoma. The gross appearance of nodes in patients with the pseudolymphoma syndrome is non-specific. Diagnostically the differentiation between malignant lymphoma and hydantoin-induced pseudolymphoma can be made upon withdrawal of the drug. Histologically it may be quite difficult to distinguish between these two entities. Because of the few cases of lymphoma appearing in patients receiving hydantoin therapy, this association may appear fortuitous but a tenfold increase over the expected incidence of malignant lymphoma has been reported in epileptic patients on hydantoin therapy. Although this does not prove that lymphoma is caused by hydantoins, it is suggested that the clinician should be aware of the association.

- 5791 **DISTINCTIVE BANDED MARKER CHROMOSOMES OF HUMAN TUMOR CELL LINES.** (Eng.) Nelson-Rees, W. A. (Univ. California, Sch. Public Health, Naval Biomedical Res. Lab., Oakland, Calif. 94625); Flandermeyer, R. R.; Hawthorne, P. K. *Int. J. Cancer* 16(1):74-82; 1975.

The Q and G banding of chromosomes was studied in nine human tumor cell lines (five breast carcinomas and four sarcomas) in order to identify the cell lines and to aid in monitoring their specificity. The range and modal number of chromosomes in at least 20 metaphases of each cell culture were established, initially. Q banding revealed, as expected, absence of a Y chromosome in cells from females. At least 15 metaphases of each cell culture were studied after trypsin-Giemsa banding. Unique groups of abnormal chromosomes ("markers") were found in each cell line when their karyotypes were constructed. A maximum of five markers was followed in all metaphases of individual cell lines at different passage levels. The possible origins of the five marker chromosomes are described for each cell line. In two instances, cultures of the same line, but in use in different laboratories and passage levels, were studied and found to have identical markers. The nine cell cultures studied will acquire new markers through rearrangements of the chromosomes or lose an occasional marker, however consistent monitoring of the chromosome banding patterns can serve to distinguish them from each other and potential contaminants such as HeLa cells or newly established cell lines.

- 5792 **COMMON VARIABLE IMMUNODEFICIENCY, HODGKIN'S DISEASE, AND OTHER MALIGNANCIES IN A NEWFOUNDLAND FAMILY.** (Eng.) Buehler, S. K. (Fac. Med., Mem. Univ. Newfoundland, St. Johns, Canada), Fodor, G.; Marshall, W. H.; Firme, F.; Fraser, G. R.; Vaze, P. *Lancet* 1(7900):195-197; 1975.

A large inbred family is described in which there were seven cases of Hodgkin's disease, three of lymphosarcoma, two of thymoma, two of common variable immunodeficiency, and single cases of retino-

blastoma, neuroblastoma, and rhabdomyosarcoma. This is the largest familial aggregate of Hodgkin's disease cases ever described. No other lymphoma cases were found for the past decade in the Newfoundland area in which the family lived. Further study of this family may help to define the genetic basis for development of Hodgkin's disease and other disorders.

- 5793 **OVARIAN CANCER IN A MONOZYGOTIC TWIN PAIR.** (Ger.) Siebers, J. W. (Universitäts-Frauenklinik, D-78 Freiburg i. Br., Hugstetter Strasse 55, West Germany); Warkentin, B.; Bender, K.; Vogel, W. *Geburtshilfe Frauenheilkd.* 35(2):107-111; 1975.

Stage IV solid adenocarcinoma was diagnosed in a 64-yr-old woman, and stage III operable, slightly differentiated, glandulopapillary adenocarcinoma of both ovaries was found two mo later in her homozygous twin sister. Metastases were found in both patients. The paramesonephric epithelium of the celom is discussed as the possible origin of the disease. The concordance of the disease in the same environment points to genetic factors as more important in the development of these two carcinomas. The only known malignant tumor that ever occurred in the family was a carcinoma of the colon in a brother. A clearcut heredity trait cannot be defined at this time.

- 5794 **POSTERIOR FOSSA SCINTIANGIOGRAPHY: DOCUMENTATION OF GENETIC PENETRANCE OF VON HIPPEL-LINDAU SYNDROME IN A CLINICALLY UNAFFECTED GIRL AND HER FATHER.** (Eng.) Hattner, R. S. (Univ. California Medical Center, San Francisco, Calif. 94143). *J. Nucl. Med.* 16(9):828-830; 1975.

The 16-yr-old clinically normal daughter of a patient with the von Hippel-Lindau syndrome demonstrated a vascular posterior fossa lesion on scintiangiography. Both patients were injected with 15 mCi ^{99m}Tc -diethylenetriaminepentacetic acid, and a timed sequence of scintiphotos were obtained at 4-sec intervals in the posterior projection. One and three hours after administration of the radiopharmaceutical, static scintiphotos were obtained. The vascular midline posterior fossa lesions of the father and daughter were both minimally evident in the blood pool scan, and even less apparent in the delayed images. These cases suggest that posterior fossa scintiangiography is a useful noninvasive diagnostic tool to screen families with von Hippel-Lindau syndrome for the associated brain lesion.

- 5795 **NON-ONCOGENIC SEQUELAE OF CANCER CHEMOTHERAPY.** (Eng.) Jaffe, N. (Children's Cancer Res. Foundation, Inc., 50 Binney St., Boston, Mass. 02115). *Radiology* 114(1):167-174; 1975.

The delayed effects of anticancer drugs and late complications in 334 long-term survivors of childhood cancer are reviewed. Sequelae associated with chemotherapy are uncommon. Two men in the series

exhibited disorders in reproductive function, possibly due to chlorambucil. A third male patient had cyclophosphamide-induced hematuria which persisted for two years after cessation of therapy. Other abnormalities were renal, hepatic, skeletal, and cardiopulmonary, ascribed chiefly to radiotherapy, although the deleterious effect of drugs on irradiated organs cannot be excluded. The data indicate that the skillful and judicious application of chemotherapeutic agents produces a minimum of delayed consequences.

5796 T-CELL MEMBRANE CHARACTERISTICS OF "MYCOSIS CELLS" IN THE SKIN AND LYMPH NODE. (Eng.) van Leeuwen, A. W. F. M. (Univ. Medical Centre, Leiden, Netherlands); Meijer, C. J. L. M.; de Man, J. C. H. *J. Invest. Dermatol.* 65(4):367-369; 1975.

A study of the atypical cells isolated from the lymph nodes and skin lesions of three patients with mycosis fungoides is presented. In all three male patients, age 57-80 yr, the diagnosis of mycosis fungoides was made on clinical and histopathological criteria. Two patients experienced infiltrates throughout the dermis, whereas one had band-shaped infiltrate. Skin biopsy and venous blood samples were processed for electron microscopy. Rosette tests were performed on mononuclear cells isolated from the lymph nodes, skin lesions, and blood. Contrary to the findings in the skin lesions and the lymph node, no atypical cells were found in the blood samples. Electron microscopy of rosettes prepared by the E-rosette procedure showed some variation in the type of the central cell. Mononuclear cells, but no monocytes or polymorphonuclear leukocytes, were seen in the rosettes. In rosettes prepared by the EAC-rosette procedure, the majority of the central cells had the morphological characteristics of monocytes; white cells with mycosis-cell characteristics were never seen. The demonstration that the atypical cells formed rosettes with uncoated sheep RBC, but not with antibody-complemented-coated sheep erythrocytes, suggests T-cell membrane characteristics of the atypical cells.

5797 RIBOSOME-LAMELLA COMPLEXES IN NEOPLASTIC HEMATOPOIETIC CELLS. (Eng.) Brunning, R. D. (Univ. Minnesota Health Sci. Cent., Minneapolis); Parkin, J. *Am. J. Pathol.* 79(3):565-578; 1975.

The ultrastructural cellular inclusions referred to as ribosome-lamella complexes were observed in the neoplastic cell population of four patients with three types of hematopoietic malignancy, monocytic leukemia, Waldenstrom's macroglobulinemia, and chronic lymphatic leukemia. The ultrastructural characteristics of the inclusions were similar in all cases. The percentage of cells affected ranged from approximately 90% in one patient with monocytic leukemia to approximately 10% in the patient with Waldenstrom's macroglobulinemia. The complexes appeared to originate from the rough endoplasmic reticulum. The observations suggested a developmental sequence beginning with aggregate

strands of rough endoplasmic reticulum, subsequent alignment of the strands of rough endoplasmic reticulum in a concentric configuration, followed by maturation to fully developed ribosome-lamella complexes. Although the ribosome-lamella complex has been reported previously in the neoplastic cells of several patients with leukemic reticuloendotheliosis ("hairy cell leukemia"), its occurrence in these three different hematopoietic disorders indicates a lack of diagnostic specificity of this structure.

5798 EPIDERMOID CYSTS, POLYPOSIS COLI AND GARDNER'S SYNDROME. (Eng.) Leppard, B. (St. Mark's Hosp., London, England); Bussey, H. J. R. *Br. J. Surg.* 62(5):387-393; 1975.

One hundred and ninety-six members of 15 families with Gardner's syndrome were investigated to determine the nature of the skin cyst that is associated with the syndrome. Sigmoidoscopy and biopsy of rectal polyps (if present) were performed in patients over 14 yr and the extent of polyposis was delineated by barium enema. Cysts of the skin were found in 39 of the 74 patients with polyposis. Of the other 34 possibly affected persons, 5 died of carcinoma of the colon or rectum before age 40, and 29 either had no polyps on sigmoidoscopy or were too young for sigmoidoscopy. The age at which polyps were discovered in patients who developed carcinoma was similar to those patients who suffered with bowel complications. This factor suggests that the age of onset of symptoms corresponds to the age at which malignant change took place in one or more of the polyps. Cysts that showed characteristic features of epidermoids were found in 35% of the patients diagnosed with polyposis. The number of cysts per patient varied from 1-20, with 33% having solitary cysts located on the legs, face, scalp, and arm. Results presented in this investigation revealed a correlation between the development of epidermoid cysts and the diagnosis of polyposis and Gardner's disease. Further investigation on the genetic transformation and differences existing between polyposis and Gardner's disease with the aid of clinical examination is indicated.

5799 ORIGIN AND STRUCTURE OF LEAF TUMORS INDUCED BY *UROPHLYCTIS LEPROIDES* (TRAB.) MAGN. IN *BETA VULGARIS* L. (Fre.) Caporali, L. (Universite Pierre-et-Marie-Curie, Institut de Biologie Vegetale UER 59, 12, rue Cuvier, 75230 Paris Cedex 05, France). *C. R. Acad. Sci. [D] (Paris)* 280(21): 2453-2456; 1975.

The origin and structure of leaf tumors induced by *Urophlyctis leproides* in *Beta vulgaris* L. were studied by cytological and cytochemical methods. Fungus development in the mesophyll cells results in hypertrophy with thickened membranes accompanied by regression of the chloroplasts, and degeneration of the nuclei and the cytoplasm. The adjacent cells divide into elements that multiply, then hypertrophy, thereby producing new tissue masses. The growth of the neoplastic tissue that constitutes the tumors is the result of the hypertrophy of the directly invaded cells and of the hyperplasia and hypertrophy of the

neighboring cells. The hypertrophy of the directly invaded cells can be caused either by the internal pressure exerted by the growing fungus (mechanical action) or by the activation of physiological mechanisms. The hyperplasia and hypertrophy of the neighboring cells are probably due to a single physiological action. The thickening of the cell membrane may be a defensive reaction against the pressure exerted by the fungus and also against the perforation of the cell membranes that is necessary for fungus propagation. The disappearance of the cytoplasm and of the nucleus strongly suggests that the parasite is feeding and growing on them. The loss of color and the dissolution of the cell membranes when the cells come into contact with the parasite indicate that the latter is producing an enzymatic lysis (biochemical action); however, it is likely that the tearing is also caused by the growth of mycelian forms, cysts in particular (mechanical action).

5800 MICROSCOPIC AND ULTRASTRUCTURAL STUDY OF A STEWART-TREVES TUMOR. (Fre.) Kermarec, J. (Service d'Anatomie pathologique, U.E.R. de Medecine, Chemin de Valombrose, 06100 Nice, France); Varini, J.-P. *Arch. Anat. Pathol. (Paris)* 23(3):193-198; 1975.

5801 THE ULTRASTRUCTURE OF OSTEOSARCOMA [abstract]. (Eng.) Williams, A. H. (Dept. Pathology, Univ. Southern California, Los Angeles, Calif.); Schwinn, C. P.; Parker, J. W. *Lab. Invest.* 32(3):440; 1975.

5802 PERIOSTEAL OSTEOGENIC SARCOMA -- AN ENTITY DISTINCT FROM PAROSTEAL OSTEOGENIC SARCOMA [abstract]. (Eng.) Unni, K. K. (Mayo Clinic, Rochester, Minn.); Dahlin, D. C.; Beabout, J. W. *Lab. Invest.* 32(3):438-439; 1975.

5803 SCANNING ELECTRON MICROSCOPY OF CARCINOMA AND ADENOMATOUS POLYPI OF THE COLON [abstract]. (Eng.) Siew, S. (Montefiore Hosp., Pittsburgh, Pa. 15213). *Lab. Invest.* 32(3):435; 1975.

5804 CARCINOMA IN THE GARDNER SYNDROME: A CASE REPORT. (Eng.) Burbige, E. J. (The Johns Hopkins Univ. Sch. Med. and Hosp., Baltimore, Md.); Wennstrom, C. J.; Levin, L. S.; Krush, A. J. *Johns Hopkins Med. J.* 136(2):95-97; 1975.

5805 COLONIC NEOPLASMS COMPLICATING URETERO-SIGMOIDOSTOMY. (Eng.) Lasser, A. (Yale Univ. Sch. Med., New Haven, Conn.); Acosta, A. E. *Cancer* 35(4):1218-1222; 1975.

5806 PRIMARY LUNG CANCER IN A CHEST CLINIC: DIAGNOSIS AND PROGNOSIS. (Eng.) Strunge, B. (Univ. Hosp., Odense, Denmark). *Chest* 67(1):28-31; 1975.

5807 PROGNOSTIC FACTORS IN COLON CARCINOMA: CORRELATION OF SERUM CARCINOEMBRYONIC ANTIGEN LEVEL AND TUMOR HISTOPATHOLOGY. (Eng.) Zamcheck, N. (Harvard Med. Sch., Boston, Mass.); Doos, W. G.; Prudente, R.; Lurie, B. B.; Gottlieb, L. S. *Hum. Pathol.* 6(1):31-45; 1975.

5808 PRIMARY ADENOCARCINOMA OF THE APPENDIX: A CLINICOPATHOLOGICAL STUDY OF 11 CASES. (Eng.) Qizilbash, A. H. (Henderson General Hosp., 711 Concession St., Hamilton, Ontario, Canada L8V 1C3). *Arch. Pathol.* 99(10):556-562; 1975.

5809 TWO CASES OF MAMMARY CARCINOMA IN YOUNG WOMEN. (Pol.) Sniegodski, J. (Szpital Wojewodzki im. Antoniego Jurasza, ul. M. Curie-Sklodowskiej 9. 85-094 Bydgoszcz, Poland); Soja, J. *Wiad. Lek.* 28(7):597-600; 1975.

5810 DETECTION OF INAPPARENT PRENEOPLASTIC-TRANSFORMED CELLS BY *IN VIVO* CULTIVATION OF DISSOCIATED MOUSE MAMMARY GLANDS [abstract]. (Eng.) Miyamoto, M. J. (Cancer Res. Lab., Univ. California, Berkeley, Calif.); DeOme, K. B.; Osborn, R. C. *Proc. Am. Assoc. Cancer Res.* 16:15; 1975.

5811 PATHOGENESIS OF RAT MAMMARY CARCINOMAS INDUCED BY DMBA [abstract]. (Eng.) Russo, (Michigan Cancer Foundation, Detroit, Mich. 48201); Saby, J.; Russo, J. *Proc. Am. Assoc. Cancer Res.* 16:164; 1975.

5812 A LOOK AT CURRENT CONCEPTS OF THE ORIGINS OF PHOSPHORUS AND CALCIUM DISTURBANCES IN CASES OF BONE METASTASIS IN BREAST CANCER. (Fre.) Chauvergne, J. (Fondation Bergonie, 180, rue de Saint-Genes, F 33076 Bordeaux-Cedex., France); Duran, M. *Bordeaux Med.* 8(5):477-481; 1975.

5813 SUPRATENTORIAL GLIOMAS IN CHILDREN [abstract]. (Eng.) Parker, J. C., Jr. (Univ. Kentucky Med. Cent., Lexington, Ky.); Mortara, R. H.; McCloskey, J. J.; Hollander, J. L. *J. Neuropathol. Exp. Neurol.* 34(1):92; 1975.

5814 PRENATAL EXPOSURE TO STILBESTROL (DES): A COMPARATIVE STUDY OF VAGINAL AND CERVICAL ABNORMALITIES IN EXPOSED AND UNEXPOSED (CONTROL) FEMALE SUBJECTS [abstract]. (Eng.) Robboy, S. J. (Mass. General Hosp., Boston, Mass.); Herbst, A. L.; Friedlander, L.; Scully, R. E. *Lab. Invest.* 32(3):432-433; 1975.

5815 AN AUTOPSY CASE OF PRIMARY LEIOMYOSARCOMA OF THE DUODENUM WITH A STATISTICAL REVIEW OF A LARGE SERIES OF JAPANESE AUTOPSY CASES. (Jpn.) Tanimura, A. (Kurume Univ. Sch. Medicine, Kurume, Japan); Yamamoto, H.; Yamaguchi, T.; Shibata, H.; Nakashima, T.; Urabe, K. *Gan No Rinsho* 21(3):214-21; 1975.

- 5816 SOME DISPUTABLE ASPECTS OF BONE ONCOLOGY.
(Rus.) Vinogradova, T. P. (Central Inst. of Traumatology and Orthopedics of the U.S.S.R. Ministry of Health, Moscow, U.S.S.R.). *Vopr. Onkol.* 21(6):29-34; 1975.
- 5817 GLOMIOID TUMOR OF THE DUODENUM. (Rus.) Portnoi, L. M. (M. F. Vladimirovskii Moscow Region Scientific Res. Inst. and Clinic, Moscow, U.S.S.R.); Gracheva, K. P.; Kriuchkova, G. S.; Maiskii, V. B. *Ark. Patol.* 37(8):73-74; 1975.
- 5818 ADENOCARCINOMA IN A BARRETT OESOPHAGUS.
(Eng.) Farnsworth, A. E. (University Hosp. 2065 Adelbert Road, Cleveland, Ohio). *Med. J. Aust.* 1(15):470-472; 1975.
- 5819 SQUAMOUS CELL PAPILLOMA OF THE ESOPHAGUS. A CASE REPORT AND LITERATURE REVIEW. (Eng.) Harrer, W. V. (Our Lady of Lourdes Hosp., Camden, N.J.); Sprague, T. H.; Keeley, F. X. *J. Med. Soc. N.J.* 72(3):229-231; 1975.
- 5820 THE ASSOCIATION OF CARCINOMA OF THE ESOPHAGUS WITH ACHALASIA. (Eng.) Hankins, J. R. (Univ. Maryland Sch. Med., Baltimore, Md.); McLaughlin, J. S. *J. Thorac. Cardiovasc. Surg.* 69(3):355-360; 1975.
- 5821 FOCAL DERMAL HYPOPLASIA WITH KERATOCONUS, PAPILLOMATOSIS OF ESOPHAGUS AND HIDROCYSTOMAS. (Ger.) Zala, L. (Dermatologische Universitätsklinik, CH-3010 Bern, Switzerland); Ettlin, C.; Krebs, A. *Dermatologica* 150(3):176-185; 1975.
- 5822 THE FINE STRUCTURE OF AMYLOID IN A PITUITARY ADENOMA [abstract]. (Eng.) Schober, R. (Stanford Univ. Sch. Med., Calif.); Nelson, D. H.; Lubinstein, L. J. *J. Neuropathol. Exp. Neurol.* 34(1):11-112; 1975.
- 5823 CARCINOMA OF THE CERVIX UTERI FROM THE MESONEPHROS. (Cro.) Osmanagic, I. (Gynecological Clinic, 71000 Sarajevo, SFR Yugoslavia); Sofic, D.; Cvijetic, E. *Libri Oncol.* 3(4):301-305; 1974.
- 5824 ADENOID CYSTIC CARCINOMA OF THE CERVIX UTERI: REPORT OF FIVE CASES AND A REVIEW OF THE LITERATURE [abstract]. (Eng.) Graham, H. M. (Parkland Memorial Hosp., Dallas, Tex. 75235); Vellios, D. *Lab. Invest.* 32(3):447; 1975.
- 5825 A CASE OF TWO INDEPENDENT NEOPLASTIC FOCI IN THE UTERINE NECK AND ON THE SKIN. (Pol.) Masik, L. (ul. Mickiewicza 4 m. 4. 36-200 Brzozow, Poland); Biesiada, B.; Samojedny, A. *Wiad. Lek.* (7):603-604; 1975.
- 5826 HOMOLOGOUS MIXED MULLERIAN TUMORS (CARCINOSARCOMA) CONFINED TO ENDOMETRIAL POLYPS. (Eng.) Kahner, S. (North Shore Hosp., Manhasset, Long Island, N.Y.); Ferenczy, A.; Richart, R. M. *Am. J. Obstet. Gynecol.* 121(2):278-279; 1975.
- 5827 HETEROLOGIC MESODERMAL TUMOUR OF THE UTERUS OF THE TYPE OF PLEOMORPHOUS RHABDOMYOSARCOMA. (Rus.) Vlasov, V. I. (District Oncological Dispensary, Iuzhno-Sakhalinsk, U.S.S.R.). *Ark. Patol.* 37(6):81-83; 1975.
- 5828 MORPHOLOGICAL VARIABILITY OF METASTASES OF CANCERS OF THE UTERINE NECK TO LYMPH NODES. (Ukr.) Vinnits'ka, V. K. (Kiev Scientific Res. Inst. Roentgenology, Radiology and Oncology, Kiev, U.S.S.R.). *Pediatr. Akush. Ginekol.* 37(3):60-62; 1975.
- 5829 DISCHARGE FROM THE NIPPLE: SIGNIFICANCE AND TREATMENT. (Dut.) Zwaveling, A. (Academische Ziekenhuis, Leiden, The Netherlands). *Ned. Tijdschr. Geneesk.* 119(31):1209-1212; 1975.
- 5830 MULTICENTRIC BREAST CANCER: THE INCIDENCE OF NEW CANCERS IN THE HOMOLATERAL BREAST AFTER PARTIAL MASTECTOMY. (Eng.) Crile, G., Jr. (Cleveland Clinic Foundation, Ohio). *Cancer* 35(2):475-477; 1975.
- 5831 INTRACYTOPLASMIC LUMINA IN BREAST CARCINOMA: A HELPFUL HISTOPATHOLOGIC FEATURE. (Eng.) Battifora, H. (Northwestern Memorial Hosp., Wesley Pavilion, 250 E. Superior, Chicago, Ill. 60611). *Arch. Pathol.* 99(11):614-617; 1975.
- 5832 EFFECT OF ASCORBIC ACID ON RECTAL POLYPS OF PATIENTS WITH FAMILIAL POLYPOSIS. (Eng.) DeCosse, J. J. (Milwaukee County General Hosp., Milwaukee, Wis. 53226); Adams, M. B.; Kuzma, J. F.; LoGerfo, P.; Condon, R. E. *Surgery* 78(5):608-612; 1975.
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5856 EMBRYONAL RHABDOMYOSARCOMA OF THE LARYNX
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V. I. (Dept. Pathoanat. Human Tumors, Inst. Exper.
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5857 THE SOLITARY PULMONARY NODULE: TEN-YEAR
FOLLOW-UP OF VETERANS ADMINISTRATION-ARMED
FORCES COOPERATIVE STUDY. (Eng.) Higgins, G. A.
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5858 NUCLEAR AND CYTOPLASMIC ALTERATIONS IN EXPER-
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MAN [abstract]. (Eng.) Stenback, F. (Univ. Nebraska
Med. Cent., Omaha, Nebr.). *J. Ultrastruct. Res.* 50(3):
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5859 PLEURO-PULMONARY FIBROSARCOMA DEVELOPED BEFORE
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(Ita.) Cazzola, M. (Ospedale "A. Cardarelli," Naples,
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See also:

* (Rev): 5418, 5420, 5421, 5422, 5423, 5424,
5425, 5426, 5428, 5453, 5454, 5455,
5456
* (Chem): 5465, 5472, 5475, 5505, 5546, 5559,
5565, 5592
* (Phys): 5602, 5604
* (Viral): 5620, 5632, 5721
* (Immun): 5672, 5686, 5695, 5720
* (Epid-Biom): 5870, 5873, 5880

- 5860 CHILDHOOD LEUKAEMIA IN THE NETHERLANDS. RESULTS OF A QUESTIONNAIRE SURVEY FOR THE 1965-1971 PERIOD, CONDUCTED BY THE DUTCH CHILDHOOD LEUKEMIA STUDY GROUP (DCLSG). (Dut.) van der Does-van den Berg, A. (No affiliation given); de Koning, J.; de Vries, J. A.; van Zanen, G. E. *Ned. Tijdschr. Geneesk.* 119(37):1403-1408; 1975.

In a national Dutch retrospective study on morbidity and survival of children with acute leukemia (1965-1971) data from 535 patients were analysed. Acute lymphocytic leukemia (ALL) and acute basophilic leukemia (ABL) accounted for 71% and acute myeloblastic leukemia, (AML) 27% of the cases. Acute leukemia was diagnosed before the age of 6 yr in 56% of the children. The longest survivals were seen in children with ALL and ABL in the 3-5 yr age group. The survival of patients in remission with ALL and ABL appears to be increasing since 1965 (median survival in 1965: 17 mo; in 1967: longer than 24 mo).

- 5861 LINKAGE OF CENSUS AND DEATH RECORDS TO OBTAIN MORTALITY REGISTERS FOR EPIDEMIOLOGICAL STUDIES IN SWEDEN. (Eng.) Bolander, A.-M. (Nat'l. Central Bureau Statistics, Stockholm, Sweden). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 36-39.

Data derived from accumulated death records of the period 1961 to 1970 were merged, via the civil registration numbers of the individuals involved, to data derived from the 1960 Census of the Swedish population. The linked register may be used to study mortality (total or specified by cause) in any population that can be defined by means of Census data. No individual information can be extracted from the part of the mortality register emanating from the Census. The author suggests that this method may be appropriate for pilot studies of the incidence of death caused by specific classes of neoplasms. Excess frequency would indicate areas for further investigation of the appropriate population at risk.

- 5862 CANCER PATTERNS IN AUSTRALIA: 1950-1973. (Eng.) Gray, N. (Anti-Cancer Council Victoria, Melbourne, Australia). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 191-200.

An analysis is presented of information derived from national mortality statistics published by the Australian Bureau of Census and Statistics and from the Central Cancer Registry, Victoria. The rates of mortality from various types of cancer were age-adjusted and the adjusted rates for 1950 and 1973 compared in order to detect trends. The adjusted rate for stomach cancer in men was 25.76

per 100,000 in 1950 and 13.44 per 100,000 in 1973. In women the rates were (1953:1973) 13.91:6.56 per 100,000. The rates (1953:1973) for other cancers were: lung cancer--men 13.89:44.96, women 2.8:6.95; cancer of the rectum--men 6.54:6.05, women 14.09:3.80; cancer of the pancreas--men 5.39:8.08; women 3.46:4.55; cancer of the large intestine except rectum--men 13.5:13.93, women 16.5:13.59; leukemia--boys 4.07:1.07, girls 3.33:0.08; cancer of the breast--women 19.37:20.03; and cancer of the cervix--women 5.07:4.94. The author concludes that the most striking alterations in death rates from 1950 to 1973 are those of lung and stomach cancer. Since there has been little change since 1950 in the survival rate for patients afflicted with stomach cancer, the decrease reflects a real reduction in the incidence of this cancer. On the other hand, the decrease in the rate of mortality due to leukemia is probably a factor of improved treatment. Data concerning the effects of the Anti-Smoking Program on smoking trends are also included. The overall consumption of cigarette tobacco has not declined significantly over the period of the Program, although high-tar cigarettes have now virtually disappeared from the market.

- 5863 SYNCHRONOUS CELL CULTURES: APPLICATIONS AND LIMITATIONS. (Eng.) Schindler, R. (Pathologisches Institut der Universität Bern, Bern Switzerland); Schaer, J. C.; Maurer, U.; Bellwald, C. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 9-14.

The kinetic aspects of partially synchronous suspension cultures and the activity of the enzymes involved in thymidine nucleotide incorporation in synchronous cultures were investigated. Cultures of transplantable murine mastocytoma cells, with a cycle time of 7-8 hr and an S period duration of approximately five hours were used. Preincubation of cells for 48 hr in Spinner culture was followed by isotonic sucrose gradient centrifugation. Cells in early interphase were collected and suspended in sucrose-free medium. Employing a Coulter counter, cell multiplication was determined as a function of incubation time. Cultures labeled with [³H]thymidine or [³H]bromodeoxyuridine (BrUdR -³H, both at 3 x 10⁻⁵ M concentration with a specific activity of 33 Ci/M) in the presence of amethopterin (10⁻⁷ M), hypoxanthine (3 x 10⁻⁵ M) and glycine (10⁻⁴ M) were used to determine the kinetics of entry of cells into the S phase. Thymidine kinase activity was assayed using [¹⁴C]thymidine as a substrate. Similarly, the activities of thymidylate synthetase, thymidine mono- and diphospho kinase and DNA polymerase were determined. Results indicated that cellular proliferation rate was synchronous during steady state conditions. Measurements of [³H]thymidine incorporated into cellular DNA produced synchronous fluctuations over the 12 hr period tested. Cell cycle time was computed at 8.24 hr. Further experiments showed that thymidine monophosphate was incorporated into cells at the rate of 0.51 nM/hr.

Thymidylate synthetase and DNA polymerase activities were assayed at 0.53 and 0.23 nM/hr x 10⁶ cells, respectively in the presence of denatured primer DNA. The activity rates for all other enzymes were significantly higher. The activities of DNA polymerase and thymidylate synthetase paralleled cellular protein content better than the pronounced fluctuations produced by [³H]thymidine incorporation into DNA. Consequently, thymidylate synthetase and DNA polymerase are concluded not to have a regulatory effect on the rate of synthesis of DNA.

5864 THIRD NATIONAL CANCER SURVEY: INCIDENCE DATA. (Eng.) Cutler, S. J. (Editor, Biometry Branch, Div. Cancer Cause and Prevention, Natl. Cancer Inst., Bethesda, Md.); Young, J. L., Jr. *Natl. Cancer Inst. Monogr.* 41:1-454; 1975.

This monograph presents the results of a survey conducted by the National Cancer Institute's Biometry Branch on the incidence of cancer in the United States during the period 1969 through 1971. Information was collected on cancers diagnosed and/or treated during this three-yr period in seven metropolitan areas and two entire states. The number of cases diagnosed and crude and age-adjusted incidence rates are classified according to sex, race, and age and anatomic site and histologic type of the cancer. The incidence rates are expressed as number of cancers/100,000 population/yr. The seven metropolitan areas included are Atlanta, Birmingham, Dallas-Fort Worth, Detroit, Pittsburgh, San Francisco-Oakland, and Denver. The two states are Iowa and Colorado. On the basis of survey data, cancer occurs in the United States as a whole at an estimated annual rate of 300 cases/100,000 population or an estimated total of 610,000 cancers in 1970 (excluding all *in situ* carcinomas and nonmelanoma cancers of the skin). The data point to striking racial differences in the incidence of cancer of the lung, prostate, esophagus, uterus, breast, and bladder.

5865 BACTERIA IN THE ETIOLOGY OF COLON CANCER. (Eng.) Williams, R. E. O. (Bacterial Metabolism Res. Lab., Public Health Lab. Service, Colindale Ave., London, NW9 5DX, England); Hill, J. J.; Drasar, B. S. *Proc. Int. Cancer Congr. 11th.* Vol. 6 (*Tumors of Specific Sites*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 322-323.

The role of bacteria that convert bile steroids to carcinogens in the etiology of colon cancer is discussed. Anaerobic *Bacteroides fragilis* can produce the initial deconjugation of the biliary steroids. *B. spp.* and bifidobacterium can dehydroxylate the bile acid nucleus, and anaerobic *Clostridium paraputrificum* can effect a dehydrogenation reaction leading to partial desaturation of at least two of the rings in the nucleus. Some experimental evidence suggests that deoxycholic acid may be carcinogenic. The concentration of total bile acids and of deoxycholic acid correlated well with colon cancer rates in various countries. In-

dividuals in the U.K. (where there is a high incidence of colorectal cancer) tend to have bacterial strains (*bacteroides*, *bifidobacteria*, and *clostridia*) in the gut that are more active in the dehydroxylation of bile steroids, and more strains of *clostridia* that are active in nuclear dehydrogenation reactions that persons from Uganda (where there is a low incidence of colon cancer). High concentrations of fecal steroids were more common in cancer patients (41) than in controls (99); there was also considerable variation in the numbers of *C. paraputrificum* with an excess of high counts in the feces of cancer patients. Thus, the evidence suggests factors favoring the development of colorectal cancer are first, a high concentration of bile steroids in the colon, consequent on diet or some intrinsic characteristic of the individual, and second, large numbers of the bacteria that can alter the steroids to produce carcinogens.

5866 SPREAD OF A AND B TYPE AVIAN LEUKOSIS VIRUSES. (Rus.) Spatar', F. V. (No affiliation given); Dzhibilov, I. I.; Voronin, E. S. *Veterinariia* (3):49; 1975.

White leghorn chickens and hybrids were investigated for the presence of antibodies to A and B type avian leukosis virus (Rous sarcoma virus) at an age of 6-7 mo. Serum antibodies were found in 39 specimens out of a total of 166 specimens investigated. The findings do not permit conclusions on the degree of contamination.

5867 URINARY TRACT CARCINOGENESIS. (Eng.) Forni, A. (Clinica del Lavoro "L. Devoto", Univ. Milan, Milan, Italy). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 94-97.

The results of urinary cytologic 10-yr follow-up studies of 1106 workers at five dyestuff factories are reported and discussed. The workers studied had been exposed to carcinogenic aromatic amines, being engaged in the production or use of 1- and 2-naphthylamine and/or benzidine; some of the workers were still exposed to minor aromatic amines at the time of study. Exposure to the carcinogens was very different for various workers, ranging from occasional or intermittent to continuous and severe. Specimens of voided urine were collected, smeared and stained mostly at the factory and sent to the laboratory for reading. The cause of death for the 24 workers who died during the 10-yr study period was: bladder cancer, 6 cases; renal tumor, 1; lung cancer, 3; stomach cancer, 1; myocardial infarction, 3; cerebrovascular accident, 2; car accident, 1; and unknown causes, 7 cases. The number of subjects with tumors during the 10-yr study period was 34, 28 of whom were new cases and 6 were cases that had been known before beginning the study. Of the 28 new cases, 25 had a tumor of the bladder, one had multiple papillary carcinoma of the left ureter, and two had renal cancer. There were recurrences

in the six previously identified cases and in eight of the new cases. All recurrences were in the bladder. Of the 48 diagnoses of tumor or recurrence, 37 were made by cytology. Most subjects whose primary diagnosis was made at cytology were asymptomatic. The cases of carcinoma were all histologically confirmed, while the diagnosis of papilloma were often only cytoscopic. The delay in clinical confirmation, is considered to be partly due to the temporary refusal of the asymptomatic worker to undergo cystoscopy, but mostly reflects the possibility of detecting at cytology malignant changes of the epithelium in the absence of evident tumors.

- 5868 MORTALITY OF AMERICAN INDIAN URANIUM MINERS. (Eng.) Wagoner, J. K. (Nat'l. Inst. for Occupational Safety and Health, Cincinnati, Ohio); Archer, V. E.; Gillam, J. D. *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 102-107.

The incidence of respiratory cancer was investigated among a group of American Indian uranium miners, who use very little tobacco, to test the hypothesis that non-smoking uranium miners would develop a high rate of respiratory cancer after a longer induction period than smoking uranium miners. All American Indians engaged in underground uranium mining who had submitted to physical examination during the period 1950-1960 were selected for study. Detailed occupational and smoking histories had been obtained by interview at the time of examination. An intense follow-up program resulted in a loss of less than 4.1% (32) of the 776 member study group to observation. Follow-up of all study group members was attempted from the time of examination to 12/31/73. Cumulative radon daughter exposure values were calculated for each miner from the date of his first mining to each sequential month of observation through September 1968. Comparisons were made with the male nonwhite population of Arizona and New Mexico. A total of 123 deaths occurred among the Indian underground uranium miners from 1960-1973, as contrasted with the expected 123.8. Only one cause-of-death category was significantly in excess of expectation: malignant neoplasm of the respiratory system, with 11 deaths observed compared to the expected 2.58. Eight of these 11 cases suffered from small cell undifferentiated tumors; one miner had a well differentiated epidermoid tumor, and in two cases, the type of tumor was not identified. None of these respiratory cancer deaths occurred before 10 yr after the beginning of uranium mining, and none have occurred at radiation exposure levels below 360 working level months (the cumulative product of length of underground exposure in working months and the concentration of radon daughters in working levels specific for mine and calendar year). The mean induction latent period among Indians who never smoked was 19 yr compared with 13.7 yr among 15 white uranium miners with lung cancer who smoked at least 20 cigarettes/day. It is concluded that because of long induction latent periods,

20-30 yr of followup are usually necessary for assessment of occupational cancer rates. The exposure of part of the population to tumor promoting agents such as cigarette smoke, leads to premature conclusions

because accelerated tumors may be the only ones initially observed as demonstrated in this study for radiation induced respiratory cancers. It is suggested that this acceleration also applies to other industrial carcinogens.

- 5869 ANALYSIS OF VOLATILE N-NITROSO COMPOUNDS IN DRINKING WATER AT THE PART PER TRILLION LEVEL. (Eng.) Fine, D. H. (Thermo Electron Corporation, 85 First Ave., Waltham, Mass. 02154); Rounbehler, D. P.; Huffman, F.; Garrison, A. W.; Wolfe, N. L.; Epstein, S. S. *Bull. Environ. Contam. Toxicol.* 14(4):404-408; 1975.

Water supplies in New Orleans and Boston areas were analyzed for volatile N-nitrosamines at the sub $\mu\text{g/l}$ level (parts per trillion). Two procedures were used: a liquid-liquid extraction, and the adsorption of the organic fraction on carbon. Quantitative analysis and identification were carried out on a single column gas chromatograph equipped with a N-nitroso compound specific thermal energy analyzer (TEA). For the liquid-liquid extraction, a 10 μl sample of concentrate was obtained and injected onto the gas chromatograph. For the carbon adsorption technique, a Mega sample (300,000 gallons of water) and a 70-year sample (25,000 l of water) was drawn. Distilled AnalaR grade solvents and standard N-nitroso compounds were used in the recovery experiments. Solvent blanks gave no response on the gas chromatograph-TEA. Recovery efficiency of N-nitroso compounds ranged from 30% at 0.013 ppb for dimethyl nitrosamine, to 130% for 0.026 ppb for N-nitroso sarcosinate. For liquid-liquid extraction, volatile N-nitrosamines were not present down to 0.001 $\mu\text{g/l}$ level (1 part per trillion). For the carbon extracts, volatile N-nitrosamines were not detected to 10 $\mu\text{g/l}$ (0.01 part per trillion). Volatile gas chromatographic-amenable N-nitroso compounds, therefore, are not present in drinking water at ultra trace levels. These results refer only to gas-chromatograph-amenable N-nitroso compounds, and nothing can be inferred for thermally labile N-nitroso compounds.

- 5870 CARCINOGENS IN THE AFRICAN ENVIRONMENT. (Eng.) Warwick, G. P. (Nairobi Medical Sch., P. O. Box 30588, Nairobi, Kenya); Linsell, C. A. *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 211-214.

Carcinogens in the African environment are considered in relation to primary hepatocellular carcinoma, Burkitt's lymphoma, nasopharyngeal carcinoma, Kaposi sarcoma, carcinoma of the cervix and penis, bladder, lung, and esophageal cancer, and esophageal cancer in cattle. Primary hepatocellular carcinoma is endemic in all areas south of the Sahara. A recent

food survey in the Murang'a district of Kenya confirmed a significant association between levels of aflatoxin B₁ ingested and the incidence of hepatocellular carcinoma. Evidence has accumulated for an association between hepatitis B antigen and cirrhosis and hepatocellular carcinoma. Hepatitis B antigen has been detected in high frequencies in adult Africans from Senegal, Ghana, Nigeria, Ethiopia, and Mozambique; it is much less common in Europe and U.S. It is suggested that aflatoxin B₁, hepatitis B antigen, or both, could be causative agents for hepatocellular carcinoma. High titers of the Epstein-Barr virus are associated with Burkitt's lymphoma but the virus alone probably cannot cause the tumor in man. The distribution of the lymphoma has also been related to the holoendemicity of malaria. Patients with nasopharyngeal carcinoma often show high levels of antibody to at least one antigen associated with Epstein-Barr virus. In Kenya where Burkitt's lymphoma is common, the two tumors are seen often in different tribes in different locations. The frequency of Kaposi's sarcoma is high in Africa with an apparent focus in northeastern parts of the Congo basin which spreads into western Uganda. A herpesvirus resembling a cytomegalovirus, has been found in tissue cultures of Kaposi's sarcoma from Zaire and Uganda patients. Cancer of the cervix is the most common cancer in women in tropical Africa. Herpes simplex II is associated with a significant number of cervix cancer cases. The recent discovery of a nitrosamine in vaginal discharge material also suggests the possibility of a chemical cause. The high incidence of bladder cancer in Egypt, Zambia and Malawi is possibly associated with urinary bilharzias. In some areas such as western Kenya and southern Uganda there appears to be only limited association with the distribution of *Schistosoma hematobium*. Among Africans in Africa lung cancer is usually rare but is increasing in frequency among those who have acquired Western smoking habits. Esophageal cancer in Africa shows greater variation in frequency than any other type of cancer. Various suggestions as to etiology include smoking air-dried tobacco, drinking beer made from maize, the presence of nitrosamines in foodstuffs and drinks, tannins, and metal and vitamin deficiencies.

5871 BERYLLIUM: PROPOSED OCCUPATIONAL SAFETY AND HEALTH STANDARD. (Eng.) Anonymous. *Fed. Regist.* 40(202):48814-48827; 1975.

A new standard for occupational exposure to beryllium is proposed and background information relating to the development of this standard is presented. The proposed new standard reduces the current permissible employee exposure for an 8-hr time-weighted average concentration, based on a 40-hr work week to 1 µg beryllium/m³ of air, sets a 5 µg/m³ of air ceiling limit for exposure to airborne concentrations of beryllium, eliminates the peak concentration level, and proposes that no employee may be exposed by skin or eye contact to bulk forms of beryllium. Beryllium sulfate and beryl ore produced lung tumors in rats following inhalation. Beryllium oxide and beryllium sulfate produced lung cancer in monkeys following intrabronchial implantation or inhalation. Zinc beryllium silicate, beryllium metal, and beryllium phosphate produced bone tumors in rabbits

following iv administration. In a study of the relation of duration of employment and previous respiratory illness to respiratory cancer among beryllium workers, 6 cases of lung cancer occurred among 142 cases of beryllium-related bronchitis and pneumonitis, for an age-adjusted lung cancer mortality rate of 284.3/100,000 as compared to the rate of 77.7 for all white males employed in the same beryllium production facility. Another study reported on the complications of beryllium disease among 535 individuals. Of 14 subjects known to have developed cancer in this group, three had bone cancer as compared to an expected rate of .05-0.1 cases. In another study 7 of 76 cases of chronic beryllium disease died from malignancy, four from cancer of the lung. The proposed new standard also sets regulations for exposure monitoring and measurement, methods of compliance, respiratory protection, emergency situations, skin protection and work clothing, equipment and clothing laundering maintenance, housekeeping, hygiene facilities and practices, medical surveillance, employee training and information, and recordkeeping.

5872 MACROMOLECULAR, CELL POPULATION-DEPENDENT CONTROL OF THE CELL CYCLE. (Eng.) Epifanova, O. (Inst. Molecular Biology, USSR Acad. Sciences, Moscow, USSR); Abuladze, M.; Zosimovskaia, A.; Smolenskaia, I. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 3-8.

The pattern of ribosomal RNA (rRNA) synthesis controlling the initiation of DNA replication was compared in two different physiological states of Chinese hamster cells: in continuously dividing cells, and after the induction of cell proliferation in quiescent cells. In addition, the sensitivity of these two cell populations to several antineoplastic agents was tested. The addition of actinomycin D (AMD, 0.08 µg/ml) to the cultures at the beginning of G₁ and its subsequent contact with cells caused a marked delay in the onset of DNA synthesis. The effect was less pronounced when AMD was added in the second half of G₁. A one-hour pulse with AMD in early G₁ produced a considerable delay in the commencement of DNA synthesis, while a pulse in the second half only slightly affected the process. In similar experiments, lucanthone (9 µg/ml) delayed the entry of cells into the S phase after a one-hour exposure in early G₁; however, inhibition of rRNA synthesis when a cell had proceeded more than two hours into the G₁ phase did not prevent the start of DNA synthesis. Inhibition of rRNA synthesis in stimulated cells at zero and two hours after the medium change prevented cells from starting DNA replication. However, after a four-hour time interval, AMD failed to prevent cells from entering the S period, and they began to synthesize DNA at a reduced rate. Even a two-hour drug pulse during the early prereplicative phase completely blocked the entry of the cells into the S period; a similar pulse in the second half of the prereplicative period exerted a delaying effect. Proliferating cells were more sensitive to antineoplastic agents (bleomycin, daunorubicin, dista-

mycin A, and imuran) than quiescent cells. Daunorubicin (5 µg/ml) completely inhibited the mitotic activity by the third hour of treatment; imuran (100 µg/ml) caused only a 15% depression, even after ten hours of contact with the cells. These experiments demonstrate that at least a part of rRNA essential for the onset of DNA replication is produced in the first half of G1, whereas the other part is made in the previous cycle and inherited from the parental cell, and imply that after the cells proceed into a quiescent state, they lose features characteristic of continuously dividing cells. Thus, their control systems may respond differentially to external factors.

5873 CELL PROLIFERATION IN WALKER TUMOUR GROWING IN THE STOMACH WALL. (Eng.)

Broyn, T. (Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway). *Cell Tissue Kinet.* 8(5):413-422; 1975.

The relationship between tumor growth, cell proliferation, and cell loss in Walker tumors growing in the gastric wall was studied. Subcutaneously growing Walker 256 tumor cells were harvested and implanted in the gastric mucosa of female Wistar rats. Ip injection of 3 mg vinblastine/kg was utilized in arresting mitosis; ip injection of 1 µCi ³H-TdR/g served to label cells. The average tumor cell population examined for estimation of the mitotic rate was 4126 cells, while an average of 3588 cells/animal was counted for estimation of labeling indices. The tumor grew and infiltrated the lamina propria and the submucosal space within seven days; necrotic areas were found in the main tumor mass after 12-14 days. The mitotic rate was highest in the tumor in the lamina propria, lowest at the periphery, with statistically significant rate differences. A tendency towards a decrease in mitotic rate in all tumor parts with increasing age was noted, and fitted a Gompertz function. The general growth pattern was a high rate of proliferation in the lamina propria, with decreasing rate in the main tumor mass, and a further significant decrease at the periphery; the mitotic rates, labeling indices, and number of grains per labeled cell all exhibited the same tendency. The method of tumor implantation suggested a stimulatory interaction between the tumor cells and the epithelial glandular cells in the lamina propria. It is suggested that the experimental tumor growth pattern may be similar to the clinical pattern of spontaneous tumor growth.

5874 HISTOLOGICAL VARIATIONS OF TUMOURS IN DIFFERENT COUNTRIES OF AFRICA. (Eng.)

Templeton, A. C. (Univ. Minnesota Medical Sch., Minneapolis, Minn.). *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 207-209.

5875 BREAST FEEDING AND BREAST CANCER. (Eng.)

Anderson, J. D. (Dept. Radiotherapy, Univ. Orange Free State, Bloemfontein, Republic of South Africa). *S. Afr. Med. J.* 49(13):479-482; 1975.

5876 MAMMARY CANCER AND GESTATION. (Hun.) Juhasz, L. (Szabolcs-Szatmar County Council Hosp., Hungary). *Mag. Onkol.* 19(3):148-153; 1975.

5877 NON-MELANOMA SKIN CANCERS: TREATMENT AND INCIDENCE IN THE DALLAS-FORT WORTH AREA.

(Eng.) Alkek, D. S. (Douglas Plaza, 8226 Douglas Ave., Dallas, Tex. 75225). *Cutis* 16(4):671-674; 1975.

5878 EPIDEMIOLOGY OF CHILDHOOD CANCER IN PIEMONTE AND VALLE D'AOSTA DURING 1965-1969.

(Ita.) Pastore, G. (Istituto di Anatomia Patologica, Università di Torino, Turin, Italy); Terracini, B. *Tumori* 61(3):291-304; 1975.

5879 MALIGNANT LYMPHORETICULAR DISEASES AT KENYATTA NATIONAL HOSPITAL IN 1973.

(Eng.) Ogada, T. (Dept. Medicine, Univ. Nairobi, Kenya). *East Afr. Med. J.* 51(12):824-828; 1974.

5880 TUMORS OF THE ACCESSORY SALIVARY GLANDS: STUDY OF 116 CASES. (Fre.) Brocheriou, C. (Groupe Hospitalier Pitie-Salpetriere, 75634 Paris Cedex 13, France); Laudénbach, P.; Bakir, A.; Seghir, M. *Arch. Anat. Pathol. (Paris)* 23(2):117-122; 1975.

5881 THE EPIDEMIOLOGICAL TOOL IN THE SEARCH FOR VIRUSES IN HUMAN TUMORS. (Fre.)

de-Thé, G. (Centre international de Recherche sur le Cancer, 150, cours Albert-Thomas, F 69008 Lyon, France). *Bull. Cancer (Paris)* 62(2):151-160; 1975.

5882 SIZES OF POPULATION NEEDED TO DETECT AN INCREASE IN DISEASE RISK WHEN THE LEVELS OF RISK IN THE EXPOSED AND THE CONTROLS ARE SPECIFIED: EXAMPLES FROM CANCER INDUCED BY IONIZING RADIATION. (Eng.) Goss, S. G. (Nat'l. Radiological Protection Board, Harwell, Didcot, Oxfordshire, OX 11 0RQ, England). *Health Phys.* 29(5):715-721; 1975.

5883 PRELIMINARY ASSESSMENT OF SUSPECTED CARCINOGENS IN DRINKING WATER. (Eng.)

Anonymous. (Environmental Protection Agency, Washington, D.C. Office of Toxic Substances); 39pp., 1975. [available through National Technical Information Services, Washington, D.C. Document No. PB-244 415/6WJ]

5884 GROWTH OF NORMAL AND LEUKEMIC MURINE WBCS IN DIFFUSION CHAMBER (DC) CULTURES [abstract]. (Eng.) Miller, A. M. (Beth Israel Hosp., Boston, Mass.); Marmor, J. B.; Russell, J. L.; Robinson, S. H. *Clin. Res.* 23(3):341A; 1975.

See also:

- * (Rev): 5417, 5420, 5425, 5427, 5428, 5430, 5431, 5432, 5433, 5434, 5435, 5436, 5437, 5439, 5440, 5441, 5443, 5446, 5453, 5456, 5457, 5458, 5459, 5460
- * (Chem): 5464, 5466, 5481, 5546
- * (Phys): 5599, 5600
- * (Path): 5776

MISCELLANEOUS

- 5885 THE ROLE OF ADENOSINE TRIPHOSPHATE, CHALONES, AND SPECIFIC PROTEINS IN CONTROLLING TUMOR GROWTH FRACTION. (Eng.) Harris, J. W. (Lab. Radiobiology, Univ. California, San Francisco, Calif. 94143); Wong, Y. P.; Kehe, C. R.; Teng, S. S. *Cancer Res.* 35(11/Part 1):3181-3186; 1975.

The role of energy supply, endogenous growth inhibitors (chalones), and specific proteins in controlling tumor growth fraction (the proportion of cells in the proliferative cell cycle) was investigated in Ehrlich ascites tumor cells carried in 8- to 12-wk-old female Swiss-Webster mice by weekly ip inoculation of 10^7 cells. Ascites cells were collected without exposing them to oxygen. ATP was extracted and assayed with hexokinase or firefly extract. Soluble proteins, isolated from tumor cells that were exposed to labeled amino acids *in vivo*, were analyzed by polyacrylamide gel electrophoresis. Lactate dehydrogenase activity was measured spectrophotometrically, and ornithine decarboxylase was measured as $^{14}\text{CO}_2$ released per microgram protein per hour incubation. The lactate dehydrogenase activity of Ehrlich ascites cells increased only slightly during exponential growth but rose sharply during the transition period between exponential growth and plateau phase and remained elevated at 20.7 U/mg protein throughout the plateau phase. This indicated that the tumor changes from aerobic to anaerobic between late exponential growth and early plateau phase. The cellular ATP content remained constant throughout tumor growth, indicating that the plateau-phase cells do not suffer from a deficient energy supply. Tumor-specific growth inhibitors were not detectable in cell-free ascites fluid from plateau-phase tumors. Electrophoretically identifiable soluble proteins isolated from tumor cells were qualitatively identical during early and late tumor growth. The activity of ornithine decarboxylase changed dramatically during the growth of the Ehrlich tumor. The enzyme was barely detectable in late plateau-phase tumors, but transplantation of 10^7 cells from these tumors into new mice was followed by a rapid and large increase in activity within hours. By two hours after transplantation, ornithine decarboxylase had increased several-fold, and a peak occurred at five hours. By eight hours, the activity had fallen by a factor of 2, but then rose a second time beginning at 9-10 hr and reached a maximum at 12 hr. Ornithine decarboxylase activity then decreased exponentially over the next few days. The second of the two ornithine decarboxylase increases coincides with the surge of cells from G_1 - G_0 into S phase, suggesting that this enzyme, or the polyamines that it synthesizes, may play a role in controlling the growth fraction of this cell population.

- 5886 MECHANISM OF LYMPHOMA CELL DEATH INDUCED BY CYCLIC AMP. (Eng.) Coffino, P. (Dept. Microbiology, Univ. California, San Francisco, Calif. 94143); Bourne, H. R.; Tomkins, G. M. *Am. J. Pathol.* 81(1):199-204; 1975.

mouse lymphoma tissue culture line, S49, is killed by isoproterenol, cholera enterotoxin, or prostag-

landin E_1 , inducers of cyclic AMP in these cells, or by the analog dibutyryl cyclic AMP. Cell death follows arrest in the G_1 phase of the cell cycle. Mutant subclones obtained by growing S49 cells in medium containing dibutyryl cyclic AMP were resistant to killing. These subclones were defective in cyclic AMP-mediated induction of phosphodiesterase activity and had reduced or absent cyclic AMP-dependent protein kinase. These results demonstrate that cyclic AMP may not be required for cell viability and growth; however, it is clear that kinase is required in S49 cells for growth arrest, cytolysis, and phosphodiesterase induction. The findings are discussed in relation to the possible physiologic role of cyclic AMP-induced cell death in T-cell differentiation. The S49 line is positive for Thy-1 antigen, indicative of its thymic origin. It is proposed that in the thymus, cell death is one pathway of differentiation and maturation is another. Cyclic AMP merely induces execution of one or the other of these determined programs. In S49 cells a condition is preserved in which the program has been selected but not yet executed.

- 5887 CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE AND INHIBITION OF DEOXYRIBONUCLEIC ACID SYNTHESIS *IN VITRO*. (Eng.) Rytomaa, T. (Second Dept. Pathology, Univ. Helsinki, Helsinki, Finland); Kiviniemi, K. *In Vitro* 11(1):1-4; 1975.

Cyclic AMP, dibutyryl cyclic AMP, AMP, cyclic guanosine monophosphate (GMP), theophylline, and deoxycytidine were tested for their ability to inhibit ^3H -thymidine incorporation into DNA of inbred Wistar rat bone marrow cells in short-term monolayer cultures. Cyclic AMP at 10^{-4} M/l or 2×10^{-3} M/l strongly inhibited ^3H -thymidine uptake by bone marrow DNA. However, an equally strong inhibition of DNA synthesis was observed with AMP at the same concentrations and with deoxycytidine at 10^{-3} M/l. Neither dibutyryl cyclic AMP nor cyclic GMP was strongly inhibitory to bone marrow cells at high concentrations. Inhibition of ^3H -thymidine incorporation into DNA by theophylline was detectable only at apparently toxic concentrations. Since inhibition of DNA synthesis was not unique to cyclic AMP, the actions of high concentrations of cyclic AMP, AMP, and other effective test substances of cultured rat bone marrow cells are essentially pharmacological in nature.

- 5888 CYCLIC AMP, A NONESSENTIAL REGULATOR OF THE CELL CYCLE. (Eng.) Coffino, P. (Dept. Microbiology, Univ. California, San Francisco, Calif. 94143); Gray, J. W.; Tomkins, G. M. *Proc. Natl. Acad. Sci. USA* 72(3):878-882; 1975.

The effect of cyclic AMP (cAMP) on growth regulation in cultured S49 mouse lymphoma cells was investigated using flow-microfluorimetric analysis. Cloned S49 cells in exponential growth were treated with 0.2 mM theophylline and various concentrations of N^6, O^2 -dibutyryl AMP (Bt₂cAMP) (0.1 mM, 0.03 mM, or 0.01 mM), and the cell density was measured as a function of

time. The cell density continued to increase at the same rate as the control (doubling time of 17-18 hr) for approximately one generation time and then remained constant. The growth arrest occurred when the cell number was double that present at the time of drug addition, regardless of the initial cell density, so long as the culture began in exponential growth. After 24 hr of treatment the cells were fully viable, as measured by trypan blue exclusion and the resumption of growth on resuspension in fresh growth medium. After 48 hr, the viability was about 20-50% and declined readily thereafter. The growth inhibitory effect of Bt₂cAMP on wild-type S49 cells and mutant cells resistant to cyclic AMP was compared. Treated and control cells were analysed with the flow-microfluorimeter and the phase durations were 2.1, 12.0 and 3.0 hr for T_G¹, T_S and T_G²+M, resp., in wild-type S49 cells. After treatment with Bt₂cAMP and theophylline for 24 hr, the mutant cells were unaffected in doubling time or cell cycle distribution. The wild-type cells, however, had ceased to grow and the fractions of cells in G₁ had increased from 34% to 88%. The drug produced a specific concentration-dependent block in the G₁ phase of the cell cycle while other phases of the cycle were not perceptibly altered. The cell cycle of mutant cells lacking the cyclic AMP-dependent protein kinase was not affected by the drug. Since these mutant cells maintain a normal cell cycle, even in the presence of high levels of cyclic AMP, periodic fluctuations in the levels of the cyclic nucleotide cannot be required for or determine progression through the cell cycle. It is concluded that, although in wild-type S49 cells cAMP exerts a specific block in the G₁ phase of the cell cycle, this inhibition is not required for the normal timing of the cycle.

5889 PERMEABILITY OF MITOCHONDRIAL MEMBRANES TO S³⁵-LABELED LIPOIC ACID AND THIAMINE IN WHITE RATS WITH WALKER CARCINOMA. (Rus.) Kar-pov, L. M. (State Univ., Medical Inst., Odessa, USSR); Dvuzhil'naia, E. D.; Savvov, V. I.; Anisimov, V. D. *Vopr. Onkol.* 21(8):69-73; 1975.

Mitochondrial membrane permeability to S³⁵-labeled lipolic acid and thiamine was investigated in tissues isolated from normal albino rats and from rats inoculated with Walker carcinoma. S³⁵-lipoic acid was most intensively accumulated by brain mitochondria, followed in descending order of intensity of accumulation by mitochondria of the kidney, liver, skeletal muscle, and small intestine. In tumor-bearing animals mitochondria of the liver showed the most accumulation, followed by brain, kidney, muscle, tumor, and small intestine mitochondria. Tumor development led to an overall increase in S³⁵-lipoic acid accumulation by mitochondria, particularly those of the liver, kidney, and small intestine. The relative intensity of S³⁵-thiamine accumulation decreased in the following order: small intestine, skeletal muscle, brain, kidney, liver mitochondria for normal rats, and brain, liver, kidney, small intestine, skeletal muscle for the tumor-bearing animals. In this latter group, some increase in S³⁵-thiamine accumulation was noted in brain and liver mitochondria, while

a decrease occurred in the other mitochondria, especially those isolated from the small intestine and skeletal muscle. The mitochondria of healthy rats accumulated S³⁵-thiamine three to four times more intensively than S³⁵-lipoic acid, while differences in the accumulation of those two substances by mitochondria of the tumor-bearing rats were less significant. The authors attribute the observed phenomena to a protein decrease in the mitochondria of the tumor-bearing animals, particularly in those of the skeletal muscle, kidney, and liver. These proteins were primarily transport system proteins.

5890 EFFECT OF CHOLESTEROL CONTENT ON SOME PHYSICAL AND FUNCTIONAL PROPERTIES OF MITOCHONDRIA ISOLATED FROM ADULT RAT LIVER, FETAL LIVER, CHOLESTEROL-ENRICHED LIVER AND HEPATOMAS AH-130, 3924A AND 5123. (Eng.) Feo, F. (Istituto di Patologia generale dell'Universita di Torino, Cso. Raffaello 30, 10125, Torino, Italy); Canuto, R. A.; Garcea, R.; Gabriel, L. *Biochim. Biophys. Acta* 413(1):116-134; 1975.

The effects of changes in cholesterol content on some functional and physical properties of mitochondria from Yoshida ascites hepatoma AH-130, and Morris hepatomas 3924A and 5123 were investigated and compared with mitochondria from cholesterol-enriched and fetal livers. Male Wistar rats were fed a 1:3 mixture of hypercholesterolic and stock diets during the first week of treatment, and a 1:1 mixture during the following 8-9 wk. Two to three weeks before sacrifice, the rats were fed a 3:1 mixture. The entire treatment lasted 11-13 wk. Hepatoma 5123 was transplanted monthly and used 20-25 days after transplantation; hepatomas 3924A and AH-130 were used 12-14 days and 6-7 days after transplantation, respectively. Mitochondria were isolated, and soluble mitochondrial constituents were separated from the insoluble constituents. The cholesterol to phospholipid ratio in mitochondria from hepatomas AH-130, 3924A, and 5123 was higher than in the particles isolated from adult or fetal rat livers. Nearly all the cholesterol of hepatoma mitochondria was located in membranes. In the particles isolated from hepatoma AH-130 and in liver mitochondria, there was more cholesterol in the outer than in the inner membrane. In mitochondria from cholesterol-enriched liver and hepatomas, there was a decrease in extent of hypoosmotic and phosphate-induced swelling, which was more marked in particles having higher cholesterol to phospholipid ratios. A statistically significant negative correlation existed between the cholesterol to phospholipid ratio and extent of volume or conformational changes. No significant modifications of these parameters were found in fetal liver mitochondria. Cholesterol content influenced neither K⁺ uptake by cholesterol-enriched or hepatoma mitochondria nor the respiratory increment related to this uptake. As a consequence of K⁺ uptake, total mitochondrial water exchangeable with tritiated water rose 20% while sucrose-impermeable water rose 42-48% in both adult rat liver and hepatoma AH-130 mitochondria. Water content is apparently not in-

fluenced by the cholesterol to phospholipid ratio. The ratio, however, is significantly correlated to both extent and initial rate of absorbance decrease of mitochondrial suspensions during K^+ uptake; the higher the ratio, the lower the extent and initial rate of absorbance decrease. It is concluded that increases in the cholesterol to phospholipid ratio of hepatoma mitochondria are involved in the decreased ability of these organelles to undergo swelling and conformational changes.

5891 THE SOURCE OF ESTRADIOL-17 β IN TROPHOBLASTIC NEOPLASIA. (Eng.) Dawood, M. Y. (New York Hosp.-Cornell Medical Center, 525 East 68th St., New York, N.Y. 10021). *Am. J. Obstet. Gynecol.* 123(3):286-290; 1975.

Unconjugated and conjugated estradiol-17 β (E_2) were measured in the sera of four patients with hydatiform mole at frequent regular intervals after removal of the mole, in the left and right ovarian vein blood in a patient with hydatiform mole, in the peripheral sera and serous fluid of the molar vesicles in seven cases of hydatiform mole, and in the fluid from the left and right theca lutein cyst (TLC) of a molar pregnancy. A radioimmunoassay method was used. Patients with highly elevated serum E_2 had a rapid clearance of E_2 within 24-36 hr after removal of the mole; those with minimal E_2 elevation had a slower clearance of the hormone from the circulation. Mole vesicle fluid had undetectable E_2 but a wide range of unconjugated E_2 which was usually lower than in the peripheral blood. Both ovarian vein blood and TLC fluid had higher E_2 concentrations than the peripheral blood. The results demonstrate that the ovaries are active in steroidogenesis in trophoblastic disease and contribute to the peripheral blood E_2 levels.

5892 TRANSMEMBRANE POTENTIALS AND STEROIDOGENESIS IN NORMAL AND NEOPLASTIC HUMAN ADRENOCORTICAL TISSUE. (Eng.) Lymangrover, J. (Medical Coll. Ohio, Toledo, Ohio 43614); Pearlmutter, A. F.; Franco-Saenz, R.; Saffran*, M. *J. Clin. Endocrinol. Metab.* 41(4):697-706; 1975.

To investigate the electrical properties of human adrenocortical cells, transmembrane potentials and steroidogenesis were measured in superfused slices of normal and neoplastic human adrenocortical tissue. The normal tissue was obtained from two kidney transplant donors, and the neoplastic tissue was obtained from two patients with renal carcinomas, two patients with renal adenomas, and one patient with a probable adrenal carcinoma. The fresh tissue was superfused with normal or potassium-free medium, the effluent from the tissue perfusion being analyzed to determine the corticosteroids released into the medium by the tissues. Membrane potentials were measured simultaneously using glass electrodes positioned with the aid of a dissecting microscope. The effects of exogenous ACTH and cyclic AMP on steroidogenesis and the membrane potential were also determined. The mean resting membrane poten-

tial in the normal cells was -56.7 mV, and the resting potentials in the tumor cells ranged from -48.7 to -13.2 mV. Exogenous ACTH had no significant effect on the membrane potential, but all of the cells were hyperpolarized after 30 min in K^+ -free solution; the degree of hyperpolarization was greatest in the normal cells. The addition of ACTH to the K^+ -free medium of the normal cells resulted in depolarization, but it had little or no effect on most of the tumor cells; the cells of one patient with a virilizing adenoma responded similarly to the normal cells. ACTH stimulated steroid formation in the normal cells and in those of the patient with the virilizing adenoma, but it had no effect on the other tumor cells; the effects of cyclic AMP were similar to those of ACTH. After prolonged exposure (greater than one hour) to K^+ -free medium, the sensitivity of the normal cells to ACTH was reduced. The results support the view that the membrane is a site of the regulatory effect of ACTH on the adrenal cortex.

5893 PROGESTERONE METABOLISM IN NORMAL HUMAN ENDOMETRIUM DURING THE MENSTRUAL CYCLE AND IN ENDOMETRIAL CARCINOMA. (Eng.) Pollow, K. (Institut f. Molekularbiologie u. Biochemie der Freien Universitat Berlin, 1 Berlin 33, Arnimallee 22, Germany); Lubbert, H.; Boquoi, E.; Pollow, B. *J. Clin. Endocrinol. Metab.* 41(4):729-737; 1975.

The subcellular distribution of progesterone-metabolizing enzymes in normal and neoplastic endometrium was investigated, and the relative amounts of progesterone metabolites formed at different stages of the menstrual cycle and at different degrees of tumor differentiation were measured. All tissues, obtained either by curettage or by hysterectomy, were examined histologically. The purity of subcellular tissue fractions was controlled by marker enzymes, DNA/RNA ratio or electron microscopy. Fractions were incubated with [^{14}C]progesterone (0.1 μ Ci) plus 40 nM of unlabeled steroid at 37 C in the reaction mixture. The reaction products were isolated, identified, and quantified by the preparation of chronic acid oxidation products and acetates, thin-layer chromatography, and crystallization to constant specific activity. The following metabolites were identified: 20 α -hydroxypregn-4-en-one, 20 α -hydroxy-5 α -pregnan-3-one, 20 α -hydroxy-5 β -pregnan-3-one, 5 α -pregnan-3-20-dione, and 5 β -pregnane-3, 20-dione, indicating the presence of a 20 α -hydroxysteroid dehydrogenase (20 α -HSD), 5 α -reductase and 5 β -reductase. The 20-HSD was located mainly in the endoplasmic reticulum and in outer mitochondrial membranes. 20 α -HSD cytoplasmic specific activity was comparatively low; purified nuclei and cytosol contained 1/6 and 1/18 of the activity of mitochondria and microsomes, respectively. Endometrial cell subfractions contained either 5 α - or 5 β -reductase activity; 5 α -reductase was bound tightly to the mitochondrial and microsomal membrane, while the 5 β -reductase was present only in the cytosol. In normal endometrium the enzyme activities in subcellular fractions depended on the menstrual cycle phase, while in endometrial carcinoma they depended

on the degree of tumor differentiation. The highest values of 5 α -reductase and 20 α -HSD activities were found in the early proliferative phase and mid-secretory phase, respectively. 5 α -Reductase specific activity increased with decreasing tumor differentiation; in comparison, the specific activity of 20 α -HSD decreased. The K_m for progesterone of the 20 α -HSD was significantly higher in the proliferative endometrium; K_m values for 5 α and 5 β -reductases were significantly lower during the proliferative than the secretory phase.

- 5894 POSSIBLE RELATIONSHIP OF POLY(A) SHORTENING TO mRNA TURNOVER. (Eng.) Sheiness, D. (Rockefeller Univ., New York, N.Y. 10021); Puckett, L.; Darnell, J. E. *Proc. Natl. Acad. Sci. USA* 72(3):1077-1081; 1975.

The size and base composition of shorter segments of poly(A) in HeLa cells and the steady state distribution of various sizes of poly(A) among mRNA molecules were examined. ^{32}P -labeled poly(A) purified from cells labeled for 24 hr was subjected to gel electrophoresis, and the size of various classes was estimated with markers. The poly(A) segments above 50 nucleotides were over 99% adenylic acid, with no detectable guanylic or uridylic acid. The 20-50 nucleotide class was at least 95% adenylic acid, with small but definite amounts of uridylic and guanylic acid as well as material migrating as cytidylic acid. Poly(A) grown for 3.5 generations in [^3H]adenine was subjected to polyacrylamide gel electrophoresis. Cytoplasmic poly(A) was distributed in a broad size range smaller than 50 to longer than 200 nucleotides. The distribution of radioactivity in gel electropherograms of poly(A) did not coincide directly with the numerical distribution of poly(A) units. A high proportion of mRNA molecules at steady state was terminated with considerably shortened poly(A). The lower limit in the distribution of poly(A) size was undetermined since the shortest segments of adenine labeled RNase-resistant material migrated in the region of the gel where the base composition studies indicated the presence of some nucleotides other than adenylic acid. Both poly(A) shortening and mRNA turnover appear to be inhibited by emetine, a drug that stops translation. It is possible that a random endonucleolytic attack leads to scission of poly(A) to a size below which the mRNA is unstable.

- 5895 STUDIES ON THE CONTROL OF DEVELOPMENT SYNTHESIS OF REGULATORY NUCLEOTIDES, HPN AND MS, IN MAMMALIAN CELLS IN TISSUE CULTURES. (Eng.) Rhaese, H. J. (Arbeitsgruppe Molekulare Genetik, Fachbereich Biologie, J. W. Goethe-Universität, Frankfurt am Main, West Germany). *FEBS Lett.* 53(1): 113-119; 1975.

Chinese hamster ovary cells (CHO), baby hamster kidney cells (BHK), and human lung cells, (WI 38) in tissue cultures were examined for the presence of regulatory nucleotides previously found in *B. subtilis*: highly phosphorylated nucleotides (HPN), guanosine-5'-

diphosphate-3'-diphosphate, ppGpp (MS I), and guanosine-5'-triphosphate-3'-diphosphate, pppGpp (MS II). The cells were labeled with 1 mCi $\text{H}_3[^{32}\text{P}]\text{O}_4$ and numbers were determined after trypsinization and suspension in PBS-buffer with a Coulter counter. CHO cells were grown for 48 hr at 37C and then incubated for additional 12 hr in the presence of $\text{H}_3[^{32}\text{P}]\text{O}_4$. Unusual nucleotides were detectable in formic acid extracts of these cells and the supernatant medium after separation by one-dimensional PEI thin-layer chromatography. Two of these unusual nucleotides found between the origin and guanosine triphosphate (GTP) migrated similarly to MS I and MS II. The same nucleotides were detected in the medium and in cell extracts after 2 hr of actinomycin treatment of CHO cells. Similar results were obtained when BHK cells were treated in the same manner. Two-dimensional PEI thin layer chromatography and chromatographic comparison with unusual substances found in *B. subtilis* showed that the three major substances present in formic acid extracts of CHO and BHK cells were MS I, MS II, and guanosine-5'-triphosphate-3'-triphosphate, pppAppp (HPN). The concentration of MS II and HPN IV as a function of cell number was measured in WI 38 cells. These nucleotides increased linearly with time for 36 hr. The increase from linearity occurred concomitantly with the end of logarithmic growth of WI 38 cells, indicating that both substances were synthesized in logarithmically growing and also in stationary phase cells. GTP, MS II, and HPN IV concentrations were constant and approximately the same in each cell regardless of their status (dividing or not). It is proposed that HPNs may control differentiation in mammalian cells as well as in *B. subtilis*, while the MS nucleotides may control RNA synthesis as proposed for *E. coli*.

- 5896 GLOBIN mRNA TRANSLATION ON ARTEMIA SALINA RIBOSOMES WITH COMPONENTS FROM FRIEND LEUKEMIA CELLS. (Eng.) Kramer, G. A. (Clayton Foundation Biochemical Inst., Univ. Texas, Austin, Texas 78712); Pinphanichakarn, P.; Konecki, D.; Hardesty, B. A. *Eur. J. Biochem.* 53(2):471-480; 1975.

A fractionated *in vitro* cell-free system employing brine shrimp *Artemia salina* ribosomes that have no endogenous activity for protein synthesis, but can be stimulated to produce the α and β chains of globin in a ratio that appears to reflect messenger RNA (mRNA) composition, is described. The system required components from the postribosomal supernatant and from the 0.5 M KCl ribosomal wash fraction derived from either rabbit reticulocytes or unstimulated Friend leukemia cells that produce little or no hemoglobin. The activity of mRNA and enzyme fractions from rabbit reticulocytes and Friend leukemia cells were tested in this system *in vitro* for their ability to direct the synthesis of the α and β chains of globin. The α : β chain ratio synthesized from mRNA in the rabbit reticulocyte salt wash fraction was 4:1. The corresponding value for the 9S mRNA fraction from the salt-washed reticulocyte ribosomes was 1:4, thus these two fractions appear to provide sources enriched in either α or β globin mRNA. Under all conditions tested, the ratio and amounts of peptides formed *in vitro* appear to reflect mRNA composition. Glo-

bin mRNA from dimethylsulfoxide-stimulated Friend leukemia cells when translated *in vitro* produced α and β chains in a ratio of 1:1. These peptides were formed in the same ratio in the intact cells. The results indicate that stringent positive translational control is not involved in induction of hemoglobin synthesis by dimethylsulfoxide in these cells.

5897 CHARACTERISTICS OF MESSENGER RIBONUCLEO-
PROTEIN AND PUTATIVE MESSENGER RNA FROM
EHRlich ASCITES TUMOR CELLS. (Eng.) Nakai, G. S.
(Veterans Admin. Hosp., 5901 East Seventh St., Long
Beach, Calif. 90801). *Biomedicine* 23(4):126-130;
1975.

Ehrlich ascites tumor cell messenger ribonucleoprotein (mRNP) and putative messenger RNA (mRNA) were isolated and studied. Ehrlich ascites tumor cells were maintained by weekly ip transplantation into mice. Isolation methods minimizing nonspecific interactions between RNA and proteins were used. Proteinase K was used to inactivate nucleases during putative mRNA isolation. Size distribution of mRNP and putative mRNA size distribution was determined in sucrose and dimethylsulfoxide gradients, by polyacrylamide gel electrophoresis, and in CsCl buoyant density gradients. The mRNP sedimented to 185S; putative mRNA sedimented between 50-95S, corresponding to maximum molecular weight of 6×10^6 to 25×10^6 daltons.

5898 MEMBRANE-BOUND RIBOSOMES OF MYELOMA CELLS:
III. THE ROLE OF THE MESSENGER RNA AND
THE NASCENT POLYPEPTIDE CHAIN IN THE BINDING OF
RIBOSOMES TO MEMBRANES. (Eng.) Mechler, B. (Dept.
Biochemistry, Univ. Cambridge, England); Vassalli,
P. *J. Cell Biol.* 67(1):25-37; 1975.

The nature of the membrane-bound ribosomal particles released by or resistant to ribonuclease treatment was studied and related to the length of the nascent polypeptide chains or to the presence of methionine-transfer RNA (Met-tRNA). In addition, the effects on the membrane-bound ribosomes of *in vivo* treatment with various inhibitors of protein synthesis were explored. Mild ribonuclease treatment (1 μ g/ml) of the membrane fraction of P3K cells released three types of membrane-bound ribosomal particles: (a) all the newly made native 40S subunits detected after two hours of [3 H]uridine pulse. Since after a three minute pulse with [35 S]methionine these membrane native subunits appeared to contain at least 7-fold more Met-tRNA per particle than the free native subunits, they may all be initiation complexes with messenger RNA (mRNA) molecules which have just become associated with the membranes; (b) about 50% of the ribosomes present in polyribosomes. Evidence is presented that the released ribosomes carry nascent chains about two and a half to three times shorter than those present on the ribosomes remaining bound to the membranes. It is proposed that in the membrane-bound polyribosomes of P3K cells, only the ribosomes closer to the 3' end of the mRNA molecules are directly bound, while the

latest ribosomes to enter the polyribosomal structures are indirectly bound through the mRNA molecules; (c) a small number of 40S subunits of polyribosomal origin, presumably initiation complexes attached at the 5' end of mRNA molecules of polyribosomes. When the P3K cells were incubated with inhibitors acting at different steps of protein synthesis, it was found that puromycin (4.5×10^{-4} M) and pactamycin (10^{-6} M) decreased by about 40% the proportion of ribosomes in the membrane fraction, while cycloheximide (3.6×10^{-3} M) and anisomycin (10^{-3} M) had no such effect. The ribosomes remaining on the membrane fraction of puromycin-treated cells consisted of a few polyribosomes, and of an accumulation of 80S and 60S particles, which were almost entirely released by high salt treatment of the membranes. The membrane-bound ribosomes found after pactamycin treatment consisted of a few polyribosomes, with a striking accumulation of native 60S subunits and in increased number of native 40S subunits. On the basis of these and previous observations, a model for the binding of ribosomes to membranes and for the ribosomal cycle on the membranes is proposed. It is suggested that ribosomal subunits exchange between free and membrane-bound polyribosomes through the cytoplasmic pool of free native subunits, and that their entry into membrane-bound ribosomes is mediated by mRNA molecules associated with membranes.

5899 NUCLEAR INCORPORATION OF RADIOACTIVE DNA
PRECURSORS AND PROGRESSION OF CELLS THROUGH
S: COMBINED RADIOAUTOGRAPHIC AND CYTOPHOTOMETRIC
STUDIES ON NORMAL AND LEUKAEMIC BONE MARROW AND
THORACIC DUCT LYMPH CELLS OF MAN. (Eng.) Hirt, A.
(Inst. Clinical Experimental Cancer Res., Univ.
Berne, CH-3004 Berne, Switzerland); Wagner*, H. P.
Cell Tissue Kinet. 8(5):455-466; 1975.

The nuclear incorporation rate of tritiated thymidine (3 H-TdR), the influence of DNA synthesis time on the precursor incorporation pattern, and the relation between the incorporation rate and labeled cells in different segments of S were studied. Bone marrow blast cells of five children with acute lymphoid leukemia, three children with acute myeloid leukemia, and one child with acute monocytic leukemia were investigated. Bone marrow suspensions were incubated with 3 H-TdR or tritiated deoxycytidine (3 H-dC), and brush smears were made, stained, and processed for radioautography and cytophotometry. Cells with small nuclei were found to have the lowest grain count, while cells with large nuclei had the highest median grain count. An analysis of the relative frequency of different grain counts over 218 bone marrow cells revealed that while the percentage of more heavily labeled cells increased with nuclear size, the grain counts varied within comparable ranges. Normalized results of studies on bone marrow cells of patients with untreated acute lymphoid leukemia revealed a significant increase, by a factor of 1.14-1.3, of median nuclear size during S, and maximum incorporation of 3 H-TdR in the second or third quarter of S. Similar results were noted in studies on bone marrow cells of patients with untreated acute myeloid leukemia

and acute monocytic leukemia; the duration of S phase did not seem to influence the nuclear incorporation pattern of the labeled exogenous DNA precursors. The results suggested that: (1) the median grain count of ^3H -TdR or ^3H -dC labeled cells in different segments of S represented the nuclear DNA synthesis rate; (2) the normal and leukemic cell types investigated have a similar nuclear incorporation pattern; and (3) in all cell populations, the maximum nuclear incorporation rate was reached in the second or third quarter of S.

- 5900 DIFFERENCES IN THE EFFECT OF CHICKEN EMBRYONAL RNAs AT DIFFERENT STAGES OF DEVELOPMENT ON CERTAIN SURFACE PROPERTIES OF TUMOR CELLS. (Rus.) Bronovitskii, A. I. (Minsk State Medical Inst., U.S.S.R.); Peretiat'ko, V. Iu. *Dokl. Akad. Nauk B.S.S.R.* 19(5):468-471; 1975.

The effect of chicken embryonal RNAs, extracted at different stages of embryogenesis, on the adhesion and growth pattern of Ehrlich ascites carcinoma cells was studied *in vitro*. Taking the number of tumor cells adhering to the substrate (bottom of the flask) after 3-day incubation as 100%, the numbers of adhering cells in cultures incubated with RNAs extracted from chicken embryos aged 5, 7, 9, 11, and 13 days were 140.2%, 234%, 255%, 326.9%, and 260%, respectively. While most of the cells adhering to the substrate had no cell processes (buds), and a few cells had up to two processes in the control, incubation with RNAs, especially with those obtained at the later stages of embryogenesis, significantly increased the number of cell processes as well as the number of the processes per cell. In addition, RNA-incubated cells formed larger agglomerates than cells in the control. The findings indicate chicken embryonal RNAs enhance the structural organization of tumor cell populations *in vitro*.

- 5901 REJOINING OF DNA SINGLE-STRAND BREAKS IN MAMMALIAN CELLS INCUBATED IN BUFFER OR IN MEDIUM AFTER AEROBIC OR ANAEROBIC X-IRRADIATION. (Eng.) Roots, R. (Stanford Univ. Sch. Medicine, Stanford, Calif. 94305); Smith, K. C. *Int. J. Radiat. Biol.* 27(6):595-602; 1975.

The extent to which single-strand breaks in the DNA of exponentially-growing Chinese hamster ovary cells are rejoined during aerobic incubation in either complete growth medium (MEM) or buffered salt solutions (PBS) has been investigated using an alkaline sucrose-gradient centrifugation technique to examine the DNA. Cells were immersed either in MEM or PBS and allowed to come to equilibration with either air or nitrogen. They were then x-irradiated with doses that resulted in approximately the same initial yields of DNA breaks, i.e., 4.7 and 18.8 krad for air and nitrogen, respectively. The extent of rejoining within the first 10 min of subsequent aerobic incubation was about 50% for those breaks produced by aerobic incubation in both the MEM and PBS. This compared to about 35% following the anaerobic irradiation of the cells in either medium. This slower initial rejoining rate could reflect

energy depletion in the hypoxic cells or the production of different types of DNA lesions after anaerobic irradiation. Subsequent to the initial rapid rate of rejoining, a slower rejoining rate was discernible in both anaerobically- and aerobically-irradiated medium-incubated cells. This slow process could not be studied for cells incubated in buffered salt solution due to the buffer-induced breakdown of the DNA. For this reason, it has not proven possible to demonstrate the existence of a secondary and growth medium-dependent repair process in mammalian cells analogous to that in bacteria.

- 5902 INCREASED HYALURONIC ACID PRODUCTION ON STIMULATION OF DNA SYNTHESIS IN CHICK EMBRYO FIBROBLASTS. (Eng.) Moscatelli, D. (Dept. Mol. Biol., Univ. California, Berkeley, Calif. 94720); Rubin, H. *Nature* 254(5495):65-66; 1975.

The positive correlation of the production of hyaluronic acid, a product of connective tissue, with the multiplication rate of chick embryo fibroblasts is reported. Low multiplication rates (turned-off cultures) were obtained by incubating cells for 16 hr serum-free medium at pH 6.8. Cultures were then stimulated to multiply faster (turned-on) by changing to medium (pH 7.4) containing serum and were compared with cultures to which fresh turn-off medium had been restored. The relative rates of DNA synthesis were measured by the incorporation of ^3H -thymidine into acid insoluble material in a 1-hr pulse. Cultures given medium at pH 7.4 with 1% serum had doubled the rate of DNA synthesis at 5 hr, and had increased it almost 10-fold at 10 hr. These turned-on cultures had also accumulated three times as much hyaluronic acid as the turned-off cultures at 5 hr, and eight times as much at 10 hr. When pH remained constant and serum concentration alone was varied, the turned-on cultures synthesized DNA at a distinctly faster rate than the turned-off cultures at 5 hr, and reached a 3.5-fold greater rate at 10 hr. The amount of hyaluronic acid accumulated was detectably greater in the turned-on cultures at 5 hr, and had become almost three times as great at 10 hr. These results show that the rate of cell multiplication and expression of differentiated function, as represented by hyaluronic acid production, are positively correlated with one another.

- 5903 THE APPLICATION OF THE *IN VITRO* MARROW CULTURE TECHNIQUES TO HUMAN HEMATOPOIETIC DISORDERS--WITH SPECIAL REFERENCE TO APLASTIC ANEMIA AND MYELOPROLIFERATIVE DISORDERS. (Jpn.) Yamada, H. (Nagoya Univ. Sch. Medicine, Nagoya, Japan). *Acta Haematol. Jpn.* 37(5):599-620; 1974.

Two parameters of the *in vitro* erythropoietin (EPO) responsiveness and the *in vitro* colony-forming capacity of bone marrow cells from patients with aplastic anemia and myeloproliferative disorders were studied to elucidate the defect of committed stem cells in these disorders. The *in vitro* EPO responsiveness of marrow cells in patients with aplastic anemia was greatly reduced compared to that of normal bone marrows. Marrow cells from patients with poly-

cythemia vera lacked EPO responsiveness in five cases and had diminished response in two cases. ⁵⁹Fe activity incorporated into heme, in cultures of polycythemia vera marrow, was markedly increased compared to that of normal marrow culture without EPO. Marrow cultures from patients with chronic myelogenous leukemia (CML) showed a normal EPO response in five and a subnormal response in three. The EPO response of marrow cells from patients with erythroleukemia (erythremic stage) was low in 3, normal in 4, and above normal in 1. The rate of EPO responsiveness of erythroleukemia marrows was markedly depressed for the erythroid hyperplasia in bone marrow of every case. Marrow cells from patients with erythroleukemia in the terminal leukemic stage showed near absence of EPO response. Normal human bone marrows yielded 53±30 colonies (almost exclusively granulocytic colonies) per 2 x 10⁵ cells if plated by the feeder-layer culture system and 52±16 colonies/10⁶ cells if plated by the no-feeder-layer-culture system. By the feeder layer method the number of colonies formed was reduced in the marrows of aplastic anemia and acute leukemias and subnormal in the marrows of polycythemia vera, chronic myelogenous leukemia and erythroleukemia (erythremic stage). With the no-feeder-layer system the number of colonies formed was normal or increased in the marrows of polycythemia vera, chronic myelogenous leukemia, erythroleukemia and primary acquired sideroblastic anemia. Results for aplastic anemia and acute leukemias were similar by the two methods. Colony-stimulating activity (CSA) in the sera of patients with aplastic anemia and myeloproliferative disorders were measured using C57BL mouse marrow cells or human bone marrows and correlated with the marrow colony-forming potential in these disorders. The elevation of CSA in the sera of patients with polycythemia vera was shown using human bone marrows, but not detected with mouse marrow cells.

5904 HUMAN PRIMARY MALIGNANT MELANOMA CULTURES. *IN VITRO* CELL DIFFERENTIATION TEST. (Fre.) Aubert, C. (Laboratoire de Biologie-Endocrinologie, Institut Gustave-Roussy, 94800 Villejuif, U 119 INSERM, 27, boulevard Lei Roure, 13009 Marseille, France). *C. R. Acad. Sci. [D] (Paris)* 280(13):1641-1644; 1975.

The ability of the cell-free culture medium from a cell line of malignant melanocytes derived from a human primary melanoma to transform cells *in vitro* was tested. The culture medium was sterilized and filtered, and then added to the medium of the test culture together with minimum essential medium and fetal bovine serum. Target cell lines utilized were from various sources: normal fibroblasts, fibroblast-like cells derived from three primary melanomas--two pigmented and one achromic, glial cells from a sympathicoblastoma, cells from an epithelioma of the bladder, and cells from an epithelioma of the uterus. The cell-free medium induced the reappearance of melanin producing pre-melanosome cells in the two cell lines composed of fibroblast-like cells derived from pigmented melanomas. The achromic melanoma fibroblast-like

cells were not transformed, and no changes were observed in any of the other cell lines tested. Transformation occurred only in the third or fourth subculture of the reactive cultures, and the transformation was not complete as some undifferentiated cells remained. Melanocytes in the transformed cultures had the morphological, biochemical, and karyotypical characteristics of the original primary tumor cells. The author concludes that the culture medium of malignant melanocytes contains a factor capable of inducing cell differentiation.

5905 STUDY OF THE MECHANISM OF K⁺-DEPENDENT SWELLING OF ERHLICH ASCITES CARCINOMA (EAC) CELLS. (Rus.) Polivoda, B. I. (Res. Inst. Med. Radiol., Acad. Med. Sci. USSR, Obninsk). *Biofizika* 20(1):160-161; 1975.

The effect of media containing hypertonic concentrations of potassium, sodium, calcium ions and saccharose on the swelling of Ehrlich ascites carcinoma (EAC) cells was studied by four-hour incubation. The cell volume was found to be a function of the hypertonicity of the medium. It was dependent not only on the concentration gradient but also of the type of agent applied. Increasing the potassium ion concentration to 20 mM did not cause any noteworthy change in the cell size, while both sodium ions and saccharose considerably attenuated the potassium ion-dependent swelling in the same concentration. The potassium ion-induced swelling was inhibited considerably by calcium ion concentrations as low as 5 mM. It is concluded that calcium ions strengthen, and potassium ions weaken, the cell membranes.

5906 ROLE OF CERTAIN HEAT-TREATED CANCER EXTRACTS ON CELL PROLIFERATION. (Fre.) Rouyer, M. (Institut Pasteur, 25, rue du Docteur Roux, 75015 Paris, France); Rouyer-Mugard, H. *C. R. Acad. Sci. [D] (Paris)* 280(4):447-449; 1975.

The effect of extracts of solid tumors, mice mammary tumors, Ehrlich adenocarcinomas, and ascites cells from mice with the Ehrlich tumor on tumor growth was studied. Some of the extracts were subjected to temperatures of 48 C for 2 hr before injection into tumor-bearing mice; solid Ehrlich tumor extracts were heated to temperatures of 55 for 2 hr, 80 C for 1 hr, or held at 48 C for 48 hr. Heated extracts of the solid tumors resulted in death of the treated animals within 1 month whereas mice injected with unheated extracts of mouse mammary tumors survived for more than a year. Prolonged heating or heating at higher temperatures increased the mitogenic activity of the solid Ehrlich tumor extracts. Mice injected with heated extracts of ascites cells from an Ehrlich tumor experienced tumor regression until the 10th post-injection day when small nodules appeared at the sc injection site. Nodules grew rapidly and resulted in death of animals in about 1 month. Electrophoretic studies of the extracts indicates a correlation between presence of DNA and lack of inhibitory activity on cancer cell proliferation.

- 5907 LOSS OF CLONOGENICITY IN AGAR BY DIFFERENTIATING ERYTHROLEUKEMIC CELLS. (Eng.) Preisler, H. D. (Dep. Med. A, Roswell Park Mem. Inst., Buffalo, N.Y.); Lutton, J. D.; Giladi, M.; Goldstein, E.; Zanjani, E. D. *Life Sci.* 16(8):1241-1252; 1975.

Colony formation by differentiating Friend erythroleukemic cells in soft agar was studied. Dimethyl sulfoxide (DMSO) (2% vol/vol) was added to the culture medium for four days. The erythroleukemic cells were then suspended in agar-medium, after which 1 ml was transferred to dishes with or without conditioned medium. Inclusion of DMSO in the culture medium of the erythroleukemic cells temporarily interfered with the initiation of DNA synthesis which occurs when these cells are seeded in fresh growth medium. However, the number of cells present in control and DMSO-containing cultures was equal after four days. The proportion of cells synthesizing DNA in control cultures was maximal within 24 hr of seeding. In DMSO-containing cultures, the proportion of DNA synthesizing cells was maximal 48 hr after seeding. When [^3H]thymidine was continuously present between the 24th and 48th hr of culture, 98% of the control cells and 92% of the cells in DMSO-containing cultures were labeled. After four days growth in the presence of DMSO, colony-forming efficiency was only 1% that of control cultures. DMSO temporarily prevents the majority of erythroleukemic cells from initiating DNA synthesis.

- 5908 EXPERIMENTAL STUDIES ON REGULATION OF ERYTHROPOIESIS *IN VITRO*. (Jpn.) Miura, Y. (Jichi Medical School, Tochigi-ken, Japan); Mizoguchi, H. *Acta Haematol. Jpn.* 37(5):589-598; 1974.

The differentiation of erythroid cells was studied using a tissue culture method. Spleen and bone marrow cells from transfusion-induced, polycythemic mice were cultured. Marrow cells were cultured with erythropoietin (EP) as follows: bone marrow masses on a plastic dish without dispersing the cells, added with liquid medium; bone marrow suspension; and reconstructed marrow masses obtained by centrifugation. The heme synthesis rate, measured using radioiron incorporation, in the reconstructed marrow was similar to that in the undispersed marrow but lower in the suspension culture. In another experiment, the spleen of the polycythemic mouse was cut into two halves. The heme synthesis rate was higher with EP in the capsule obtained by crushing half a spleen from a polycythemic mouse with saline, than in the other parts of the spleen. More erythropoietin-responsive cells (ERC'S) may be localized in this part of the spleen. The spleen capsule may have provided the most favorable microenvironment for embedding of ERC'S since the embryonic stage. The formation of erythroid cells may be greatly influenced by the cell-to-cell interaction of the precursor cells. In untreated acute leukemia, colony formation of the marrow cells was low. The marrow cells from acute myeloblastic leukemia patients showed low or no response to EP; the cells from acute lymphocytic leukemia patients maintained nearly normal response to EP. To investigate the mechanism of suppression of hemopoiesis in leukemia,

leukemic cells were added to the culture of non-leukemic cells. There was a significant suppression of colony forming activity when one tenth the number of leukemic cells was added to the culture. Response to EP was also suppressed when one half the number of leukemic cells was added to the culture.

- 5909 DIFFERENCES IN THE INCORPORATION OF BROMODEOXYURIDINE BY HUMAN LYMPHOBLASTOID CELL LINES. (Eng.) Henderson, E. E. (Dept. Microbiology, Univ. Chicago, Chicago, Ill. 60637); Strauss, B. *Cell* 5(4):381-387; 1975.

Long term human lymphoblastoid lines were tested for their ability to grow in medium containing bromodeoxyuridine (BrdU) and to incorporate analog into their DNA. Eight Burkitt's lymphoma cell lines divided at least twice in BrdU (3.0×10^{-5} M)-containing medium, and made DNA in which over 90% of the thymidine residues were substituted with analog in both strands. Three infectious mononucleosis-derived lines and 24 lines transformed *in vitro* were inhibited by BrdU after one cell division and made only hybrid DNA in which one strand was substituted with analog. One out of eight normal individuals from whom long term lines were prepared gave cell lines which divided at least twice in BrdU and gave DNA in which both strands were substituted with analog. It would appear that intrinsic cellular factors regulate the response to BrdU and that Burkitt's tumor lines are characterized by their ability to make stable doubly substituted DNA containing a high proportion of halogenated analog.

- 5910 AGE AT FIRST BIRTH: A VARIABLE WITH SINGLE, DOUBLE OR EVEN TRIPLE SIGNIFICANCE IN MAMMARY CANCER. (Fre.) Juret, P. (Centre Francois-Baclesse, Route de Lion-sur-Mer, F 14018 Caen, France); Couette, J. -E.; Brune, D.; Vernhes, J. -C. *Bull. Cancer (Paris)* 62(2):165-174; 1975.

A study is presented of the relation of age at birth of first child and the appearance and development of a mammary neoplasm. Data was obtained in a 4 yr study on 790 women, 237 nulliparous and 553 parous women, treated for breast cancer at the Francois Baclesse Center in Caen, France. Statistical analysis ($p < 0.001$) revealed that age at first pregnancy had a direct relation to the age when the breast neoplasm occurred. Cancer appeared at about the same age in nulliparous women and women whose age at first birth was 29 or 30. When data analysis was limited to parous females in whom neoplasm occurred after 45 yr of age, the relation of age of pregnancy to age of appearance of the neoplasm was still direct but statistical significance decreased ($p < 0.02$). Obstetrical histories were also obtained on 742 females who survived three yr after surgery for breast neoplasms and 633 who survived for five yr. Data analysis revealed a lower survival rate among women who gave birth to five or more children as compared to the nulliparous group and the group with one to four live births. Results indicate

that pregnancy at an early age and multiparity are unfavorable risk factors in evolution of the single mammary neoplasm. In order to reconcile results of this study with studies which state incidence of mammary neoplasms is lower for females who have early pregnancies, the authors hypothesize that early pregnancy releases factors that inhibit the mechanism of induction of the neoplasm but once the neoplasm occurs, accelerate its development.

- 5911 EXCRETION OF 5-S-CYSTEINYLDOPA IN THE URINE OF HEALTHY SUBJECTS. (Eng.) Agrup, . (Dep. Dermatol., Univ. Gothenburg, Sweden); alck, B.; Fyge, K.; Rorsman, H.; Rosengren, A. M.; osengren, E. *Acta Derm. Venereol. (Stockh.)* 55 (1):7-9; 1975.

Seventy-six Caucasians, 30 men and 46 women, were investigated for the 24-hr excretion of 5-S-cysteinyldopa in the urine during the months of September to November, 1973. No subject had had strong sun exposure for at least four weeks. A preliminary finding of a variation of 5-S-cysteinyldopa with season necessitated this precaution. The excretion varied between 9.0 and 242 $\mu\text{g}/24$ hr. The mean value in men was 100 $\mu\text{g}/24$ hr and in women, 7.8 $\mu\text{g}/24$ hr. Subjects with white hair had lower values than those with pigmented hair, but there was no other difference between the excreted amounts in subjects with differing hair color. There was no variation with age when the subjects with white hair were excluded. No variation with wt or body surface was found. Excretion of dopa and dopamine determined together did not correlate with the excretion of 5-S-cysteinyldopa. These observations will provide a basis for interpreting urinary 5-S-cysteinyldopa values in patients with suspected malignant melanoma.

- 5912 FORMATION OF CYSTEINYLDOPA FROM GLUTATHIONEDOPA IN MELANOMA. (Eng.) Agrup, . (Dep. Dermatol., Univ., Gothenburg, Sweden); alck, B.; Kennedy, B. M.; Rorsman, H.; Rosengren, A. M.; Rosengren, E. *Acta Derm. Venereol. (Stockh.)* (1):1-3; 1975.

Glutathionedopa metabolism was studied *in vivo* in mice and in homogenates of guinea-pig kidney and of human malignant melanoma tissue. Glutathionedopa injected into mice was metabolized and excreted in the urine as a compound with the fluorescent characteristics of cysteinyldopa. Glutathionedopa incubated with a guinea-pig kidney homogenate was metabolized to a compound with the fluorescent characteristics of cysteinyldopa. Boiling of the kidney homogenate prevented the metabolism of glutathionedopa. Incubation of glutathionedopa with a homogenate of a melanoma metastasis led to the formation of a compound with the fluorescent characteristics of cysteinyldopa. Boiling of the melanoma homogenate prevented the metabolism of glutathionedopa. Large amounts of glutathione added to the incubate inhibited the reaction. Lung tissue and blood plasma had no detectable ability to metabolize glutathionedopa. The results show that human melanoma contains

one or several enzymes capable of metabolizing glutathionedopa to a smaller dopathioether, probably cysteinyldopa. Such enzymes seems to be normally present in mice and guinea-pigs and have been demonstrated in the guinea-pig kidney.

- 5913 CHANGES IN MICROTUBULE PHOSPHORYLATION DURING CELL CYCLE OF HELA CELLS. (Eng.) Piras, R. (Instituto de Investigaciones Bioquímicas "Fundación Campomar", Obligado 2490, Buenos Aires (28), Argentina); Piras, M. M. *Proc. Natl. Acad. Sci. USA* 72(3):1161-1165; 1975.

Protein kinase activity and endogenous phosphorylation of tubulin were examined in synchronously growing HeLa cells at different times after release from a double thymidine block. The S phase, as measured by the rate of DNA labeling with [^3H] thymidine, began immediately after the release from the thymidine block, and lasted for 6-8 hr with a maximum at 4 hr. The highest percentage of mitotic cells (14%) occurred 12 hr after the release from the thymidine block, but the peak was relatively broad (6-8 hr). The protein phosphokinase activity, measured as the rate of casein phosphorylation, and the maximal tubulin phosphorylation of the microtubular fraction of cells harvested at different times after release from thymidine block, were compared with the cytoplasmic protein phosphokinase activity. The increase in protein phosphokinase activity of the microtubular fraction during late G₂ and M (8-14 hr) did not parallel any detectable change in the cytoplasmic fraction. An increased maximal phosphorylation of tubulin was also observed in late G₂ and M. The specific activity of the protein phosphokinase of the microtubular fraction showed a three-fold increase in the mitotic cells and a minor but consistent increase also in the G₂ cells. In *in vivo* studies, HeLa cells were cultured in a phosphate deficient medium containing $^{32}\text{P}_i$ for a period which began approximately two generations before synchronization and lasted until the cells were collected at the different stages of the cell cycle. The microtubular fractions obtained from cells in the S and M stages of the cycle contained twice as much protein-bound phosphate as those arising from G₁ and G₂ cells. The variable phosphate content of tubulin through the cell cycle suggests that such covalent modification might be important to enable tubulin to carry over some of its functions during the cell cycle.

- 5914 SERUM-FREE GROWTH OF HTC CELLS CONTAINING GLUCOCORTICOID- AND INSULIN-INDUCIBLE TYROSINE AMINOTRANSFERASE AND CYTOPLASMIC GLUCOCORTICOID RECEPTORS. (Eng.) Thompson, B. E. (Natl. Cancer Inst., Bethesda, Md. 20014); Anderson, C. U.; Lippman, M. E. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):403-411; 1975.

Successful establishment of lines of HTC cells grown in chemically defined medium without macromolecular supplements is described. HTC-serum free 1, uncloned wild type (SF HTC-327), derived from third serial subcloning of HTC⁺; and SF HTC-H1 (inducible clone selected for growth in mercaptopurine), were

derived from serum free cell lines of wild type HTC. Cells were grown in improved minimal essential medium - zinc option (IMEM-ZO). Amino acid requirements were studied by growth measurements in IMEM-ZO, each culture lacking a single amino acid. Cells were also tested for growth in varying concentrations of amino acids. Induction of aminotransferase by dexamethasone, insulin, or serum was measured. The lines adapted to serum-free growth were SF HTC-327 and SF HTC-H1. In appearance and manner of growth, they greatly resembled their serum-grown counterparts. HTC-SF1, SF HTC-327, and SF HTC-H1 could survive at least one week in the absence of serine, asparagine or isoleucine. Without isoleucine, cells lived about a week, yet in the absence of serine or asparagine cell growth continued for several months. The relative optimum concentration of each amino acid is the concentration of each amino acid found in the IMEM-ZO medium to which they had been adapted. The two clonal lines retained inducible aminotransferase similar to that in wild type serum grown HTC cells, although the absolute level of enzyme was lower. The induction by glucocorticoids over basal levels was similar to serum grown cells. Dexamethasone was a slightly more potent inducer than hydrocortisone. HTC cells show a dose dependent response to actinomycin D and other agents which block RNA synthesis. Insulin or serum caused a 20% increase in existing aminotransferase activity after two hours. The induction of the enzyme with glucocorticoids implied the presence of cytoplasmic steroid receptor proteins in the serum free cells. Saturation levels of receptors for dexamethasone were found to be 0.13-0.14 pM/mg of cytoplasmic protein in the supernatant fraction of SF HTC-H1 and SF HTC-327.

5915 NUCLEAR PHOSPHOPROTEIN KINASE ACTIVITIES IN NORMAL AND NEOPLASTIC TISSUES. (Eng.)

Thomson, J. A. (Univ. Texas System Cancer Center, Houston, Tex. 77025); Chiu, J. -F.; Hnilica, L. S. *Biochim. Biophys. Acta* 407(1):114-119; 1975.

Nuclear phosphoprotein kinases from normal adult Sprague-Dawley rat liver and transplantable neoplasms were fractionated and compared. Extracts of nuclei from normal rat liver, containing both phosphoproteins and phosphoprotein kinases, were applied to phosphocellulose columns and eluted by steps with 0.1, 0.3, 0.5, 0.7, and 0.9 M NaCl in Tris buffer. Kinase activity in the eluted fractions was detected by monitoring the incorporation of [γ - 32 P]-ATP into endogenous material. One peak of activity was observed with each elution stage. Similar elution profiles were obtained when extracts of nuclei from Novikoff hepatoma, Ehrlich ascites, or Walker carcinoma cells were treated identically, except that an extra small peak, representing 3 to 12% of the total incorporation, eluted in the 0.3 M NaCl step. Unlike the other enzyme fractions, the incorporation of 32 P-ATP by material in this peak was greatly stimulated (138 to 400%) by the presence of Mn^{2+} . The addition of heat-inactivated phosphoprotein from the nuclei of Ehrlich ascites cells also increased the incorporation by a very large factor (950 to 1500%); most of the material phosphorylated

under these conditions migrated electrophoretically in polyacrylamide gels as one band, although several minor bands were also seen. The incorporation was not stimulated by heat-inactivated phosphoprotein from normal rat liver, nor were the other enzyme fractions able to phosphorylate the material derived from the Ehrlich ascites cells. The authors conclude that both a unique protein kinase fraction and a specific phosphoprotein substrate are present in the nuclei of cells derived from neoplastic but not normal tissues.

5916 ISOLATION AND CHARACTERIZATION OF ALKALINE PHOSPHATASE-CONSTITUTIVE VARIANTS FROM CHINESE HAMSTER OVARY CELLS (CHO-K1). (Eng.)

Nose, K. (Inst. Medical Science, Univ. Tokyo, P.O. Takanawa, Tokyo-108, Japan); Katsuta, H. *J. Cell. Physiol.* 86(2/Suppl. 1/Part 1):253-260; 1975.

The isolation of clones of high alkaline phosphatase (ALP) activity from ALP-negative Chinese hamster ovary (CHO-K1) cells and some properties of the clones are reported. CHO-K1 cells were cultured in Eagle's MEM supplemented with 5% fetal calf serum and 0.1 mM each of non-essential amino acids. Clones were histochemically stained. ALP-positive cells were stained red and their frequency of occurrence was determined. Pure clones were isolated from ALP-positive clones by the use of micro test plate. For some tests, cells were sonically disrupted and the lysate was centrifuged. The supernatant was used as an enzyme source to assay the activities of ALP-I, ALP-II, and acid phosphatase. Extracts were prepared from adult Chinese hamster liver, kidney, intestine, and femur by mincing and homogenizing. Specimens for chromosome analysis were prepared by the dropping and flaming technique. CHO-K1 clones, treated with various concentrations of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) for two hours revealed increased numbers of ALP-positive cells with increased concentrations of MNNG. Consistent alterations in chromosomes were observed in all ALP-positive clones, disappearance of two small metacentric chromosomes and increase in the number of submetacentric chromosomes. Enzyme activities in the clones AL-151, AL-323, and AL-431 revealed an increase in the level of ALP-I activity of several hundred-fold, while ALP-II activity increase 3-4-fold as compared with their activity in parent CHO-K1 cells. Extracts of various organs were prepared and the sensitivity of ALP to heat and L-homoarginine was tested. ALP of liver and intestine was unstable at 50 C and was not inhibited by L-homoarginine in contrast to that of bone and kidney.

5917 PLACENTAL ALKALINE PHOSPHATASE: REGULATION OF EXPRESSION IN CANCER CELLS.

(Eng.) Fishman, W. H. (Tufts Univ. Sch. Medicine, Boston, Mass. 02111); Singer, R. M. *Ann. N.Y. Acad. Sci.* 259:261-272; 1975.

The effects of prednisolone and hyperosmolarity on HeLa TCRC-1 (a cell line monophenotypic for the Regan isoenzyme of alkaline phosphatase) and HeLa TCRC-2 (monophenotypic for nonRegan alkaline phos-

phatase) were compared, and their possible significance in relation to cell cycle was investigated. The FL amnion cell line was also included in some of these studies. Alkaline phosphatase was measured using disodium phenylphosphate as a substrate. For polyacrylamide gel electrophoresis, the sonicated cell suspension was diluted 1:1 with a 20% sucrose and 1.0% Triton X-100 solution prior to the application to the gel. Cultures were inoculated with 500×10^3 cells/flask, and prednisolone (1 $\mu\text{g/ml}$) was added 24 hr later. Both HeLa cell lines had a significantly lower growth rate in the continued presence of prednisolone. The alkaline phosphatase activity in HeLa TCRC-1 increased during the growth cycle, reaching its maximum level at day 9. Hormone treatment greatly increased enzyme activity, which reached a maximum at day 4 and continued through day 8. There was little effect of prednisolone on enzyme activity in the HeLa TCRC-2 cell line through day 6, after which enzyme activity decreased in the presence of hormone. Hormone enhancement occurred in 3 of 4 lines (FL amnion, HEP-2: a carcinoma cell line, HeLa TCRC-1 and TCRC-2). In all cases, the enhanced electrophoretic band had the properties of the Regan isoenzyme. An intestinal-type alkaline phosphatase was also found in the HEP-2 and FL cell lines, which was diminished by hormone treatment. Hyperosmolarity enhanced enzyme activity in both HeLa TCRC-1 and FL amnion cell lines. When cells were grown in hyperosmolar medium plus prednisolone, the resulting increase in specific activity in both cell lines was higher than for the individual inducing agent alone. The isoenzyme profiles of HeLa TCRC-1 were not altered by induction. FL amnion cell line did reflect an altered isoenzyme profile when grown under hyperosmolar conditions similar to that resulting from hormone treatment. The authors suggest that the effect of both of these inducing agents occurs when the cells are in the S period, and with the arrest of further DNA synthesis, a secondary effect is the accumulation of the cells at a period of elevated synthesis of the Regan isoenzyme.

5918 ELECTROPHORETIC STUDY OF PHOSPHOFRUCTOKINASE ISOENZYMES FROM HUMAN TISSUES AND TUMOURS OF THE NERVOUS SYSTEM. (Eng.) Bennett, M. J. (R. Infirm. Sheffield, England); Taylor, C. B.; Timperley, W. R. *Eur. J. Cancer* 11(5):359-363; 1975.

The distribution of phosphofructokinase isoenzymes was investigated in extracts of a variety of normal human adult tissues, in 17 gliomas, and in fetal brains ranging in age from 14-42 wk, by polyacrylamide disc gel electrophoresis. At least four forms of enzymes were observed. None of the adult tissues was identifiable by a single species of enzyme. Fetal brain up to 28 wk contained one band (band III). Liver contained the two most cathodal enzymes (bands III and IV), while skeletal and cardiac muscle contained the three most anodal bands (I, II and III). Brain contained the two intermediate bands (II and III). Seven out of eight grade IV astrocytomas contained bands II, III, and IV; whereas the better differentiated gliomas showed the same pattern as adult normal

brain. This change in enzyme profile appears not to be a reversion to a fetal form.

5919 CARCINOFOETAL ALTERATIONS IN GLYCOGEN PHOSPHORYLASE ISOZYMES IN RAT HEPATOMAS. (Eng.) Sato, K. (Hirosaki Univ. Sch. Medicine, Hirosaki, Japan); Sato, T.; Morris, H. P.; Weinhouse, S. *Ann. N.Y. Acad. Sci.* 259:273-286; 1975.

Isozyme patterns of glycogen phosphorylase in rat hepatomas and rat tissues during development are discussed as part of a continuing study on the loss or retention of enzymes involved in specific hepatic functions in a series of rat liver neoplasms. A phosphorylase isozyme, distinguishable kinetically, immunologically, electrophoretically, and by isoelectric focusing from liver and muscle types, is commonly present in various rat hepatomas; these include Novikoff, Morris, and Yoshida hepatomas. This isozyme is also the sole type in the placenta and early embryo, and in liver and muscle is replaced with the organ specific liver and muscle types during development. In other organs (heart, stomach, spleen, lung, uterus, small intestine, kidney, and testis) the replacement of the fetal phosphorylase is only partial; this type is especially retained. Almost all hepatomas retain what appears to be the liver phosphorylase as well as the fetal type, as demonstrated by their requirement for both AMP and sulfate. It is suggested that this isozyme is a prototype whose appearance in hepatomas is one of many examples of carcinofetal alterations in isozymes. It is also suggested that because the fetal isozyme may be retained as a normal adult isozyme in some tissues, its appearance in cancer is not only a carcinofetal expression, but may also be considered to result from the breakdown of the rigid regulatory mechanisms that control the tissue-specificity of protein synthesis. This impairment of gene control may also be responsible for the pattern of tumor progression that occurs unpredictably but inevitably as tumors grow or metastasize.

5920 EFFECT OF HUMAN LYSOZYME (MURAMIDASE) ON POTASSIUM HANDLING BY THE PERFUSED RAT KIDNEY: A MECHANISM FOR RENAL DAMAGE IN HUMAN MONOCYTIC LEUKAEMIA. (Eng.) Mason, D. Y. (Radcliffe Infirmary, Oxford, England); Howes, D. T.; Taylor, C. R.; Ross, B. D. *J. Clin. Pathol.* 28(9):722-727; 1975.

The effect of purified human muramidase on renal potassium excretion was studied in the isolated, perfused rat kidney. The hemoglobin-free perfusion medium consisted of 6.7 g % of dialyzed bovine serum albumin, fraction V, in Krebs-Henseleit saline, gassed with 5% CO₂:95% O₂. Glucose (5 mM) was the only added substrate. Muramidase (1-600 $\mu\text{g/ml}$) was added to the perfusion medium after a control period of 40 min. [¹⁴C]insulin clearance, urinary Na⁺ and K⁺ were determined at ten-minute intervals. Samples for the analysis of muramidase content in urine and perfusion medium were taken at ten-minute intervals so that each kidney served as a control for the determination of Na⁺ reabsorption and K⁺ excretion in the presence and absence of muramidase. The

kidney was divided into samples for the determination of wet wt/dry wt ratio and for the chemical determination of muramidase. A portion was also fixed in 10% formalin for histochemical detection of muramidase. Addition of muramidase to the perfusion medium resulted in its recovery at increased concentration in the urine, and its disappearance from the medium at a linear rate. At increasing concentrations of muramidase, excretion increased linearly as the filtered load increased. Reabsorption of muramidase, which was 96.5% at a medium content of 1 µg/ml muramidase, fell to 62.8% when the filtered load was 94 µg/min (medium muramidase concentration, 600 µg/ml). No tubular maximum for muramidase reabsorption was observed even at these very high medium concentrations. The concentration of muramidase in each kidney was four to five times the final concentration in the perfusion medium. Histological localization of muramidase within the kidney showed intense staining beneath the luminal pole of the cells lining the proximal tubing. Little or no material was seen in the glomeruli or the distal tubular cells. When muramidase was added to the perfusion medium there was an immediate increase in the excretion of K⁺ in the urine. The stimulation of K⁺ excretion was observed at all concentrations of muramidase to a similar extent but even the highest doses did not produce a net excretion of K⁺. At the lowest concentrations of muramidase, sodium reabsorption was unaffected, but at concentrations over 75 µg/ml there was a measurable inhibition of reabsorption. It is suggested that the hypokalemia seen in some patients with myelomonocytic leukemia may be directly attributed to an elevated circulating muramidase level which promotes increased urinary K⁺ excretion.

- 5921 STIMULATION OF DNA POLYMERASE BY FACTORS ISOLATED FROM NOVIKOFF HEPATOMA. (Eng.) Probst, G. S. (Dept. Biol. Sci., Univ. Cincinnati, Cincinnati, Ohio 45221); Stalker, D. M.; Mosbaugh, D. W.; Meyer, R. R. *Proc. Natl. Acad. Sci. USA* 72(3): 1171-1174; 1975.

Factors isolated from extracts of Novikoff hepatoma cells which are capable of stimulating *in vitro* RNA synthesis several fold are identified. The activity can be resolved into three separate protein peaks on DEAE-Sephadex. Two of these, factors II and III, were purified and partially characterized. Both factors increased the initial rate of rat liver cytoplasmic DNA polymerase synthesis and allowed synthesis to proceed much longer. If either factor was added after synthesis by the DNA polymerase had reached a plateau, resumption of synthesis occurred. The factors appeared to have different modes of action or sites of action since they showed an additive effect even when a single one was used at saturating conditions. These factors were present in normal rat liver but at a concentration less than 5% of that found in the tumor cells. When tested with several highly purified DNA polymerases (DNA nucleotidyltransferase), the factors showed a much greater stimulation of homologous, nonmitochondrial enzymes (rat liver nuclear-, rat liver cytoplasmic-, or Novikoff-DNA polymerases) when compared with rat liver or calf liver mitochondrial-, *Escherichia coli* I-, or

sea urchin nuclear-DNA polymerases. The mechanism of action of these factors is not known at present. No enzymatic activity has been associated with factor II. Highly purified, but not homogeneous, preparations of factor II contained low levels of endonuclease. It was not established whether endonuclease was a contaminant or was responsible for the stimulating activity.

- 5922 S-ADENOSYLMETHIONINE:PROTEIN METHYLTRANSFERASES IN HEPATOMAS. (Eng.) Paik, W. K. (Temple Univ. Sch. Med., Philadelphia, Pa.); Kim, S.; Ezirike, J.; Morris, H. P. *Cancer Res.* 35(5):1159-1163; 1975.

S-Adenosylmethionine:protein-lysine methyltransferase (protein methylase III) and S-adenosylmethionine:protein-arginine methyltransferase (protein methylase I) activities were examined in isolated nuclei and cytosol fractions from Morris and Novikoff hepatomas with different growth rates. Activities of both enzymes parallel the rates of tumor growth in fast- and moderately growing hepatomas; the parallelism was more evident with protein methylase I than with protein methylase III. The activity of ε-alkyllysine, the enzyme responsible for demethylating proteins, decreased in fast- and moderately growing tumors, in which protein methylase III activity was elevated. Thus the two enzymes are apparently physiological antagonists. When isolated rat liver nuclei were methylated *in vitro* with S-adenosyl-L-[methyl-¹⁴C]-methionine as methyl donor, nearly equal amounts of methyl-¹⁴C were incorporated in H₂SO₄-insoluble protein and histones. However, amino acid analysis revealed that methylated arginines were the predominant form of radioactivity in the H₂SO₄-insoluble protein (product of protein methylase I), while methylated lysines were the major methylated amino acids in the histones (product of protein methylase III). Furthermore, the hydrolysate of the H₂SO₄-insoluble protein showed four unknown radioactivity peaks on the amino acid analyzer in addition to the known methylated arginine and lysine derivatives. Further studies to identify these compounds are in progress.

- 5923 PARTICLE-ASSOCIATED RNA-DEPENDENT POLYMERASE AND HIGH-MOLECULAR-WEIGHT RNA IN A HUMAN CELL LINE DERIVED FROM POLYCYTHEMIA VERA BONE MARROW. (Eng.) Weimann, B. J. (Basel Inst. Immunology, Grenzacherstrasse 487, CH 4058 Basel, Switzerland); Kluge, N.; Dube, S. K.; von Ehrenstein, G.; Krieg, J. C.; Kind, J.; Ostertag, W. *J. Natl. Cancer Inst.* 55(3):537-542; 1975.

A particle fraction with a density of 1.15-1.19 g/cm³ was isolated from the cytoplasm of a human cell line (PHD) established in culture from the bone marrow of an untreated patient with polycythemia vera. Electron micrographs of cross sections of cells and cell homogenates revealed virus-like particles on which DNA could be synthesized. An RNA-dependent DNA polymerase, isolated from the particles, preferred poly(rA) x oligo(dT) over poly(dA) x oligo(dT) and was able to polymerize

deoxyguanosine monophosphate in a reaction stimulated by poly(rC) x oligo(dG). The results are compatible with the idea that RNA tumor viruses are either involved in the shift of normal to polycythemic bone marrow or of polycythemia to leukemia.

- 5924 CIRCULAR DICHROISM AND ETHIDIUM BROMIDE BINDING STUDIES OF CHROMATIN FROM WI-38 FIBROBLASTS STIMULATED TO PROLIFERATE. (Eng.) Nicolini, C. (Temple Univ. Health Sciences Center, Philadelphia, Pa.); Baserga, R. *Chem. Biol. Interact.* 11(2):101-116; 1975.

The circular dichroism (CD) spectra and binding ability of ethidium bromide were used to study the structural changes taking place in stimulated WI-38 cell chromatin. The CD spectra of unshocked chromatin and cellular nuclei of WI-38 human diploid fibroblasts were obtained on a Jasco Model J40 recording spectropolarimeter. Recently stimulated chromatin exhibited an increase in maximum positive ellipticity at $\lambda 272$ nm from 2005 degrees x cm^2/dM (average) to 2340 degrees x cm^2/dM after five minutes. The maximum positive ellipticity increased steadily until it reached 3280 degrees x cm^2/dM at 3 hr. The data, recorded between 300 and 360 nm, showed that a θ_{308} value of WI-38 chromatin, at the optimum dye/DNA-P ratio of 0.25, increased from 26500 degrees x cm^2/dM to 31500 degrees x cm^2/dM at 5 and 15 min after stimulation. A maximum of 45000 degrees x cm^2/dM was reached at four hours. Absorption spectra and spectrophotometric titrations to measure the number of primary binding sites for ethidium bromide were recorded in a Guilford 2400 spectrophotometer. These sites are apparently intercalated between base pairs of double-stranded polynucleotides. The number of primary binding sites for chromatin of WI-38 of unstimulated cells is $n=0.67$. The number of ethidium bromide binding sites (in percent of calf thymus DNA) for chromatin calculated from the ratios of ellipticity at 308 nm, increased from 26.6 to 31.1% within five minutes of stimulation. This value increased steadily to 46% at four hours. In a final experiment, the differences in chromatin template activity and in CD spectra between chromatin of stimulated and unstimulated cells were abolished when both chromatins were extracted with 0.25 M NaCl. The CD spectrum of DNA is unaffected by moderate concentrations of univalent salt.

- 5925 KINETICS OF INACTIVATION OF HISTONE mRNA IN THE CYTOPLASM AFTER INHIBITION OF DNA REPLICATION IN SYNCHRONISED HeLa CELLS. (Eng.) Gallwitz, D. (Physiologisch-Chemisches Institut der Universität Marburg, Lahnberge, 355 Marburg/Lahn, West Germany). *Nature* 257(5523):247-248; 1975.

The kinetics of histone mRNA inactivation in the cytoplasm after interruption of DNA replication with hydroxyurea were investigated in HeLa S-3 cells in suspension culture. The cells were synchronized by double block with 2 mM thymidine and allowed to enter S-phase by resuspension in fresh medium. Three and four hr after entering S-phase,

the cells synthesized histones at maximal rate. Cells were then treated for different times with 3 mM hydroxyurea. Histone mRNA was separated from poly(A)-containing mRNA and was quantitated by its translation in a reticulocyte lysate. Acid soluble proteins of the lysate were separated by CM-cellulose chromatography into two fractions; a globin-containing CM-1 fraction and CM-2 containing the histones. As early as ten min after blocking DNA replication about 20% of functional histone mRNA was lost from polyribosomes in comparison to the mRNA content of the third hour S-phase cells. Thirty and 60 min after arrest of DNA synthesis, less than 30% and 15%, respectively, of active histone mRNA were left on the polyribosomes. Further treatment with the blocking agent did not change this value significantly. An increase of polyribosomal histone mRNA by about 20 to 30% was seen between the third and fourth hr after entry into S-phase, which subsequently decreased again. From a semilogarithmic plot of the data, it was deduced that after a short lag of about 5 min, histone mRNA was inactivated according to first-order kinetics with a half life of about 13 min. The author suggests that the lag may represent the time required for hydroxyurea to penetrate the cells and interrupt subsequent flow of histone mRNA from the nucleus to the cytoplasm.

- 5926 CHROMATIN DIRECTED TRANSCRIPTION OF 5S AND tRNA GENES. (Eng.) Marzluff, W. F. Jr. (Dept. Biol., Johns Hopkins Univ., Baltimore, Md. 21218); Huang, R. C. C. *Proc. Natl. Acad. Sci. USA* 72(3):1082-1086; 1975.

The transcription of 5S and tRNA genes *in vitro* was studied in 66.2 mouse myeloma cells. Chromatin prepared by gentle methods retained its ability to synthesize RNA using bound endogenous RNA polymerase (RNA nucleotidyltransferase; nucleosidetriphosphate: RNA nucleotidyltransferase). The RNA was prepared after synthesis by extraction with phenol-sodium dodecyl sulfate and analyzed by sucrose density gradient centrifugation. The RNA was extremely heterogeneous in size, ranging up to 28S. When the low molecular wt RNA was analyzed by gel electrophoresis, specific RNA species were observed which were identical to 5S RNA and the 4.5S precursor to 4S RNA. Both 5S RNA and 4.5S precursor to 4S RNA were transcribed accurately and the transcription was reinitiated continually *in vitro*. Their synthesis was not inhibited by α -amanitin (1 $\mu\text{g}/\text{ml}$ as was found previously for these species in isolated nuclei. The results demonstrate that faithful RNA transcription continues *in vitro* with chromatin prepared by a gentle procedure. Despite removal of much of the nuclear protein and RNA, the chromatin retained RNA synthetic properties similar to that of isolated nuclei.

- 5927 CONFORMATIONAL STUDIES ON THE β SUBUNITS OF HUMAN HEMOGLOBIN AND THEIR ARGINYLCOOH PEPTIDES. (Eng.) Bucci, C. F. (Univ. Maryland Sch. Medicine, Baltimore, Md. 21201); Bucci, E. *Biochemistry* 14(20):4451-4458; 1975.

The physicochemical properties of the β subunits

of hemoglobin, after alkylation of the SH groups with iodoacetamide, were investigated. The β subunits of hemoglobin upon alkylation of the cysteinyl residues with iodoacetamide showed a sedimentation velocity with a sedimentation constant ($s_{20,w}$) near 1.8 for monomeric subunits. They reacted with α chains to give a tetrameric hemoglobin with an $s_{20,w}$ near 4.4. Their spectrum was indistinguishable from that of untreated β chains below 270 nm, otherwise they showed some deviation that became pronounced in the Soret region, where the optical activity of the alkylated subunits was definitely lower than that of the native subunits. Upon removal of the heme the apo- β subunits showed a decreased optical activity in the far-UV region of the spectrum indicating a substantial loss of helical content. Their sedimentation behavior was consistent with the presence of large aggregates, which dissociates into monomers upon reconstitution with cyanoheme. The apo- β subunits could be re-natured from 6 M guanidine hydrochloride. They showed a stoichiometric reaction with the heme in the molar ratio 1:1. Upon reconstitution with the heme their optical activity became similar to that of the native β chains in the far-UV region of the spectrum, but remained lower in the near-UV and Soret regions. After acylation of the lysyl residues with citraconic anhydride the apo- β subunits were digested with trypsin, and the arginyl-COOH peptides $\beta(1-30)$, $\beta(31-40)$, $\beta(41-104)$, and $\beta(105-146)$ were separated by gel chromatography. With the exception of the peptide $\beta(105-146)$, which was insoluble at neutral pH, the sedimentation behavior of the other peptides showed the presence of small polymers. The percentage of α helix, β conformation, and of random coil (or unordered structure) of the various proteins and peptides was measured fitting their CD spectra in the far-UV region. In this way the helical content of the native and reconstituted alkylated β subunits appeared to be near 76%, a value very near to that present in the same subunits in the hemoglobin crystal. The helical content of the apo- β subunits in 0.04 M borate buffer at pH 9.6 decreased to a value near 45%. The helical content of the isolated peptides in electrolyte solutions was in any case near 10% indicating an almost complete loss of the structure that they have in the hemoglobin crystal. Cyanoheme reacted with the peptide $\beta(41-104)$; however, the reaction was not stoichiometric, indicating a low affinity of the heme for the peptide. With the exception of the peptide $\beta(31-104)$, all other peptides recovered some of their helical structure when dissolved in 50% methanol. Notably also the apo- β subunits did so suggesting that the loss of structure upon the removal of the heme could be in part due to the exposure of the heme pocket to water.

- 5928 CHARACTERIZATION OF MOUSE CELLS RELEASING OR RESPONDING TO MITOGENIC FACTOR INDUCED BY PHYTOMITOGENS *IN VITRO*. (Eng.) Jacobsson, H. (Dept. Tumor Biol., Karolinska Institutet, S-104 01 Stockholm, Sweden); Blomgren, H. *J. Immunol.* 114 (5):1631-1637; 1975.

Mouse lymphocyte populations exposed to mitogen were tested for their capacity to release factors that

stimulate other lymphocytes to synthesize DNA or enhance their response to mitogens *in vitro*. Congenitally athymic (nude) CBA mice, homozygous for the nu gene (nu/nu), and BALB/c mice, heterozygous for the nu gene (nu/+), were used. Cells from lymph node, spleen or thymus from animals treated two days earlier with cortisone were cultured at concentrations of 0.5×10^6 and 2.0×10^6 cells/ml of medium. The cells were incubated with or without mitogens. Lymph node and spleen cells released more mitogenic factor (MF) than thymocytes upon exposure to concanavalin A (Con A), phytohemagglutinin (PHA), or pokeweed mitogen (PWM) *in vitro*. The T cells were largely responsible for MF production, since cell suspensions depleted of phagocytic cells did not exhibit any decreased ability to produce MF and spleen cells from congenitally athymic (nude) mice produced no detectable MF activity. The MF stimulated thymocytes, lymph node cells, and spleen cells to synthesize DNA. Spleen cells from nude mice were also stimulated. The MF released by lymphocytes in response to Con A-induced DNA synthesis of lymphocytes in itself and did not require the presence of mitogen. It is concluded that phytomitogen lectins stimulate T cells to synthesize DNA and to release soluble factor(s) which are mitogenic for both T and B cells. The B cells may thus be unresponsive to the phytomitogen, but still undergo blast transformation.

- 5929 ULTRASTRUCTURAL LABELING OF CELL SURFACE LECTIN RECEPTORS DURING THE CELL CYCLE. (Eng.) Garrido, J. (Departamento de Biología Celular, Instituto de Ciencias Biológicas, Universidad Católica de Chile, Santiago de Chile, Chile). *Exp. Cell Res.* 94(1):159-175; 1975.

The distribution of specific surface receptors in the course of the cell cycle was studied on two transformed cell lines by means of ultrastructural labeling techniques employing concanavalin A (ConA) and wheat germ agglutinin (WGA). Synchronized cultures of Cl₂TSV₅, a simian virus 40 transformed hamster cell line, and of CHO cells were labeled as monolayers or in suspension in the different phases of the cell cycle. In cells labeled in monolayers, a moderately discontinuous pattern of surface labeling was present during G₁, S, and G₂. On cells in mitosis, however, this pattern changed strikingly and became very discontinuous. These results indicate that the degree of receptor clustering is greater in mitosis than in interphase. In cells labeled in suspension, the differences in pattern between mitosis and interphase were absent. Colcemid treatment did not modify the distribution of the label, either in interphase or in mitosis. Moreover, cells in mitosis collected by Colcemid treatment and labeled at a moment in which parallel unblocked cultures had completed mitosis and passed into G₁ showed an interphase-type labeling pattern; this indicates that a certain dissociation exists between surface events and nuclear events during mitosis. These results are discussed in terms of several factors that may contribute to the production of receptor clustering, namely, direct lectin action, surface movement and membrane flow, participation of cytoplasmic structures and attachment of cells to a substratum.

- 5930 THE EFFECT OF CTAB, A CATIONIC SURFACTANT, ON THE ABSORPTION RATE OF [^{14}C]TRIPALMITATE FROM A TEST MEAL IN THE RAT. (Eng.) Isomaa, B. (Inst. of Biology, Abo Akademi, 20500 Turku 50, Finland); Sjoblom, G. *Food Cosmet. Toxicol.* 13(5):517-520; 1975.

The effect of cetyltrimethylammonium bromide (CTAB), a cationic surfactant, on the absorption rate of ^{14}C -tripalmitate from a test meal was studied in male Sprague-Dawley rats. The test meal, containing 2 μCi /rat of ^{14}C -tripalmitate and 0.8, 2.4, 8.0, or 400 mg/kg of CTAB, was administered po by stomach tube. In small doses, CTAB increased the absorption rate of tripalmitate by increasing the rate of gastric emptying. The latter increase appeared to be proportional to the amount of CTAB administered. However, the 400 mg/kg dose markedly retarded the rate of gastric emptying and also caused a marked reduction in the tone of gastric muscles. The only significant difference between control and treated animals in the amount of radioactivity recovered from the gastrointestinal wall was found in animals receiving the highest dose. In these animals, the amount of radioactivity in the wall of the small intestine was lower than in the controls. At the doses that increased the rate of gastric emptying, CTAB administered intragastrically to pylorus-ligated rats did not alter the amount of fluid secreted into the stomach. A slight increase in gastric secretion associated with the highest dose (400 mg/kg) was not sufficient to explain the inhibition of gastric emptying at this dose.

- 5931 INCORPORATION OF S^{35} -LIPOATE LABEL INTO ANIMAL TISSUE IN DIFFERENT TERMS AFTER TUMOR TRANSPLANTATION. (Rus.) Trebukhina, R. V. (Medical Inst., Grodno, U.S.S.R.); Mikhal'tsevid, G. N.; Ostrovskii, J. M.; Iakubchik, T. N. *Vopr. Onkol.* 21(7):96-100; 1975.

Albino mice inoculated with Ehrlich ascites tumor (1,300,000 cells), and male rats inoculated sc with Walker carcinosarcoma were given sc injections of [^{35}S]-labeled thioctic acid 1, 5 and 10 days after tumor transplantation to study the urinary elimination and the incorporation of thioctic acid in different tissues and organs. The animals were sacrificed 1-24 hr after injection. After an intense urinary elimination, the radioactivity, measured 24 hr after injection, increased with the interval between tumor transplantation and injection in the liver, kidney, heart, pancreas, brain, muscles, and in the carcinosarcoma in rats. A similar accumulation of radioactivity in the liver, kidney, heart, pancreas, spleen, tumor, and ascitic fluid was observed in mice. There was no significant difference between tumor-bearing and control animals concerning the urinary excretion, nor between the accumulation of the radioactivity in the tumor, ascitic fluid, and other tissues. The pyruvate dehydrogenase activity in the tumor tissue increased three-fold one hour after thioctic acid injection. The findings suggest huge reserves of pyruvate dehydrogenase activity in the tumor.

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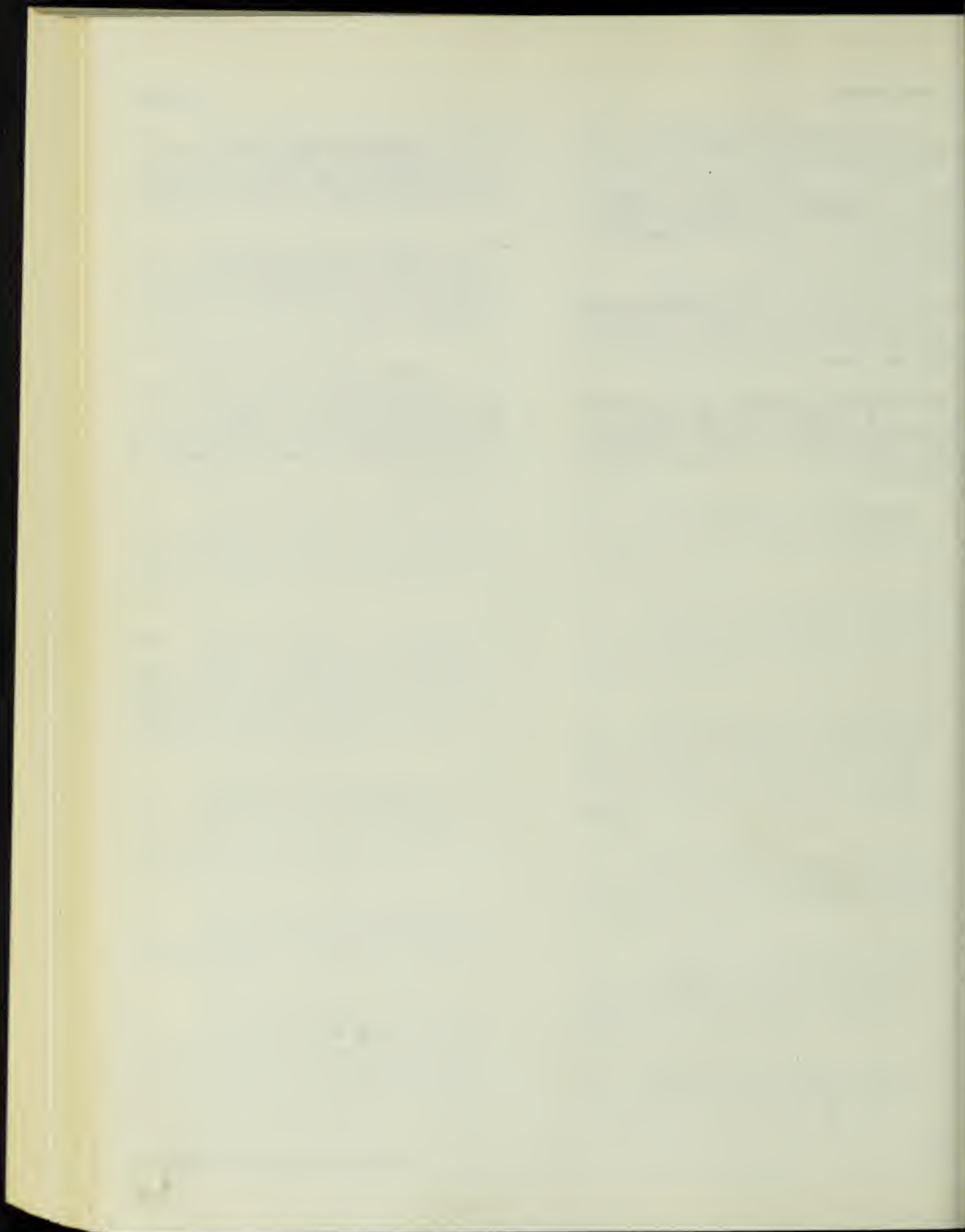
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AKAMATSU, Y. 5553*	AUPOIX, M. 5613	BENACERRAF, B. 5451*
AKAO, M. 5539*	AZUMA, T. 5738*	BENASSI, M. 5979*
AKATSUKA, T. 5934*	BABICHEV, V.A. 5657	BENDER, K. 5793
AL-ADHAMI, R. 5626	BADARACCO, G. 5979*	BENDITT, E.P. 5940*
ALEXANDER, M. 5576*	BADEN, H.P. 5589*	BENEDICT, W.F. 5521*
ALEXANDER, P. 5419	BAKAY, L. 5768	BENNETT, D. 5715
ALFRED, L.J. 5546*	BAKER, D.G. 5606*	BENNETT, M.J. 5918
ALKEK, D.S. 5877*	BAKER, J.R. 5564*	BENTVELZEN, P. 5654
ALLEN, J.M. 5835*	BAKIR, A. 5880*	BERCOVICI, J.P. 5591*
AMATI, P. 5641	BALDWIN, R.W. 5448*	BERGAN, J.J. 5417
AMES, B.N. 5402	BALIN, H. 5937*	BERGER, F.M. 5679
AMOS, D.B. 5658*	BALIS, M.E. 5503, 5520*, 5568*	BERGER, R. 5456*
ANDERSON, C.U. 5914	BANDLE, E.F. 5985*	BERKMAN, J.I. 5416
ANDERSON, D. 5469	BANFIELD, W.G. 5965*	BERNACKI, E.G. 5839*
ANDERSON, J.D. 5875*	BARBANTI-BRODANO, G. 5643	BERRY, D.L. 5548*
ANDERSON, N.G. 5447*	BARKHODAROV, R.M. 5437	BERSAY, C. 5854*
ANDREYEV, A.V. 5674	BARNES, B.A. 5417	BERTINI, M. 5618
ANISIMOV, V.D. 5889	BASERGA, R. 5924	BERTRAM, J.S. 5481
AOKI, T. 5696	BASKAR, J.F. 5944*	BHATNAGAR, R.M. 5682
AOYAGI, T. 5625	BASSIN, R.H. 5629	BICHE, P. 5779
APPELLA, E. 5692	BASTEN, A. 5681	BIESIADA, B. 5825*

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BILDER, G.E. 5722*	BRAUNSTEINER, H. 5743*	BURKE, P.J. 5691
BILLING, R.J. 5729*	BRAY, P.F. 5993*, 5995*	BUSCH, H. 5976*
BISHUN, N. 5491	BRESLER, S.E. 5605*	BUSH, I.M. 5673
BLACK, O., JR. 5472	BRIAND, P. 5590*	BUSHAR, G.S. 5675
BLACKLOW, N.R. 5608	BRIDGES, J.M. 5689	BUSSEY, H.J.R. 5798
BLACKSTONE, E. 5841*	BROCHERIOU, C. 5880*	BUTEL, J.S. 5645
BLASI, F. 5641	BRONDZ, B.D. 5674	BYAR, D. 5455*
BLEVINS, R.D. 5585*	BRONOVITSKII, A.I. 5900	BYKOVSKII, A. 5669*
BLGEMERS, H.P.J. 5630	BROOME, J.D. 5946*, 5947*	BYNUM, J.W. 5977*
BLOMBERG, J. 5638	BROWN, D.W. 5439	BYSTRYN, J.-C. 5742*
BLOMGREN, H. 5928	BROWN, E. 5967*	CAMPBELL, D., JR. 5726*
BLUMBERG, B.S. 5745*, 5786	BROYN, T. 5873	CANDREVIOTOU, S. 5964*
BLUMING, A.Z. 5706	BROZNA, J. 5932*	CANELLAKIS, E.S. 5685
BOCQUET, L. 5854*	BRUGGE, J.S. 5645	CANNON, G.B. 5700
BOENISCH, T. 5997*	BRUNE, D. 5910	CANUTO, R.A. 5890
BOGUSH, T.A. 5480	BRUNNER, K.T. 5414	CAPORALI, L. 5799
BOIOCCHI, M. 5648	BRUNNING, R.D. 5797	CARIM, H.M. 5786
BOIRON, M. 5659*, 5667*	BRUNS, G.R. 5673	CARNEGIE, P.R. 5693
BOLANDER, A.-M. 5861	BRUNTSCH, U. 5454*	CAZZOLA, M. 5859*
BOLOGNESI, D.P. 5611, 5631	BRYANT, G.M. 5501	CEROTTINI, J.C. 5414
BONNARD, G.D. 5726*	BUAFO, C.K. 5696	CESARINI, J.-P. 5775
BOOKOUT, J.B. 5615	BUBENIK, J. 5412	CHAHINIAN, P. 5723*
BOQUOI, E. 5893	BUCCI, C.F. 5927	CHAI, C.K. 5695
BOTIS, S. 5664*	BUCCI, E. 5927	CHANDRA, P. 5650
BOURNE, H.R. 5886	BUCKLEY, C.E., III 5658*	CHANDRA, S. 5665*
BOUTIBONNES, P. 5533*	BUCKLEY, P.M. 5662*	CHANG, R.S. 5690
BOUTIN, C. 5853*	BUCOVAZ, E.T. 5542*	CHANG, S.Y. 5975*
BOUTWELL, R.K. 5516	BUEHLER, S.K. 5792	CHAPMAN, A.L. 5626
BOWERS, M.P. 5546*	BUFF, K. 5959*	CHARLES, J.F. 5591*
BOYER, S.H. 5691	BUFFA, R. 5950*	CHARLESWORTH, F.A. 5431
BOYSE, E.A. 5696, 5715	BULBROOK, R.D. 5427	CHASIN, L.A. 6000*
BRAND, I. 5602	BUOEN, L.C. 5602	CHAUHAN, P.S. 5601
BRAND, K.G. 5602	BURBIGE, E.J. 5804*	CHAUVEAU, J. 5478
BRAUN, W.E. 5417	BURGER, M.M. 5688	CHAUVERGNE, J. 5812*

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CHEMNITZ, J. 5779	COLNAGHI, M.I. 5671	DE GROOT, F.G. 5654
CHEN, K. 5685	COMOGLIO, P.M. 5618	DE KONING, J. 5860
CHEN, Y.M. 5960*	CONDON, R.E. 5832*	DE LA FARGE, F. 5731*
CHERIAN, M.G. 5513	COONEY, A.M. 5510	DE MAN, J.C.H. 5796
CHERNINA, L.A. 5614	COOPER, M. 5569*	DE-THE, G. 5881*
CHEVRIER, L. 5667*	CORE, S.K. 5496	DE VRIES, F.A.J. 5660*
CHIMISKIAN, K.L. 5657	CORREA, P. 5575*	DE VRIES, J.A. 5860
CHIU, J.-F. 5915	CORTEZ, C. 5485	DEAN, J.H. 5692, 5700
CHC-CHUNG, Y.S. 5939*	COTE, M.G. 5547*	DEBOV, S.S. 5987*
CHOJNACKI, H. 5983*	COUETTE, J.-E. 5910	DECLOITRE, F. 5478
CHOPAN, M.N. 5961*	COX, K.O. 5733*	DECOSSE, J.J. 5832*
CHOUROULINKOV, I. 5727*	CRAMPTON, R.F. 5431	DEGAWA, M. 5537*
CHOUX, R. 5853*	CRAWFORD, D.H. 5621	DEKKER-MICHELSEN, M.J.A. 5630
CHOWDHURY, S. 5563*	CREASIA, D.A. 5463	DEKNUDT, G. 5527*
CHRISTEN, Y. 5445*	CRILE, G., JR. 5830*	DELLA PORTA, G. 5648
CHRISTOPHER, J.P. 5479	CROKER, B. 5628	DELLA TORRE, G. 5648
CHRISTOV, K. 5597	CUKOR, G. 5608	DELL'ACQUA, A. 5838*
CHU, T.M. 5938*	CUTLER, S.J. 5864	DEMEESTER, L.J. 5765
CHUAT, J.-C. 5659*	CVIJETIC, E. 5823*	DEMIDOVA, A.S. 5653
CHUNG, E. 5958*	DA COSTA, M. 5953*	DEMIDOVA, S.A. 5656
CHYLE, M. 5670*	DAEHNFELODT, J.L. 5590*	DEMPO, K. 5720
CHYLE, P. 5670*	DAHLIN, D.C. 5802*	DENNIS, A.J. 5758*
CIERNY, G. 5991*	DAIRMAN, W. 5959*	DEOME, K.B. 5810*
CIMADEVILLA, J.M. 5624	DALGARD, D.W. 5575*	DEPAOLI, A. 5662*
CLAESSON, M.H. 5753*	DARNELL, J.E. 5894	DESAI, L.S. 5982*
CLAIR, T. 5939*	DARRACQ, N. 5530*	DESAIVE, C. 5834*
CLAPP, N.K. 5577*, 5578*	DAUGHERTY, J.P. 5577*	DESCHATRETTE, J. 5943*
CLEMENT, J.J. 5970*	DAVEY, F.R. 5749*, 5750*	DESCHNER, E.E. 5569*
CLIVE, D. 5999*	DAVILA, J.C. 5852*	DEUMIE, M. 5507
COATES, A.S. 5693	DAVIS, J.W. 5952*	DEWEY, W.C. 5599
COFFINO, P. 5886, 5888	DAVIS, R.H. 5937*	DEWYS, W. 5455*
COGGAN, R.J. 5662*	DAWE, C.J. 5965*	DHERMY, D. 5854*
COLE, P. 5458*	DAWOOD, M.Y. 5891	DI NARO, C. 5838*

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- DJUSKALIEV, ZH.D.
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- DOOS, W.G.
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- DOUGLAS, S.D.
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- DRAHOVSKY, D.
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- DRAPER, G.J.
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- DREVON, C.
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- DRIVSHCLM, A.
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- DRIZLIKH, G.I.
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- DROLLER, M.J.
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- JROZD, J.
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- DUBE, S.K.
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- DUESBERG, P.H.
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- DUNCAN, W.P.
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- DUPONT, B.
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- DURAN-TROISE, G.
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- DURAND, M.
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- DUTTA, T.K.
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- DVUZHIL'NAIA, E.D.
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- DWORSKY, R.
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- DYSON, D.P.
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- DZHIBILOV, I.I.
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- EBENER, U.
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- EGAN, H.
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- EILBER, F.R.
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- ENGLAND, J.M.
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- ENGLE, J.F.
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- EPIFANOVA, O.
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- EPSTEIN, M.A.
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- EPSTEIN, S.S.
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- ESKIN, B.A.
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- ETTLIN, C.
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- EVANS, A.E.
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- EVANS, C.H.
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- EVANS, J.T.
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- EVERSOLE, L.R.
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- EZIRIKE, J.
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- FABIAN, E.
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- FADEEVA, T.A.
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- FAIVRE, E.
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- FALKENSAMER, M.
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- FARNSWORTH, A.E.
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- FASAL, E.
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- FEDOROVSKAYA, M.I.
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- FELDMAN, J.D.
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- FELDMAN, J.M.
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- FENYO, E.M.
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- FEO, F.
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- FERENCZY, A.
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- FERNANDES, G.
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- FICHARDT, T.
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- FIERS, W.
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- FIGUEIREDO MENDES, N.
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- FINE, D.H.
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- FINK, U.
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- FIRME, F.
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- FISCHINGER, P.J.
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- FISHER, B.
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- FISHER, C.
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- FISHMAN, W.H.
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- FLADERER, H.
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- FLANDERMEYER, R.R.
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- FLAVELL, R.A.
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- FLAXMAN, B.A.
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- FLINT, S.J.
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- FODOR, G.
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- FOLEY, G.E.
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- FONT-SOTO, D.
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- FORD, G.H.
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- FORNI, A.
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- FORNI, G.
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- FORTNER, G.W.
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- FOX, J.E.
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- FRAENKEL-CONRAT, H.
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- FRANCO-SAENZ, R.
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- FRANKS, J.J.
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- FRANZESE, S.
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- FRASER, G.R.
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- FRAUMENI, J.F., JR.
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- FREIDLANDER, L.
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FRIDMAN, W.H. 5775	GISSELBRECHT, S. 5629	GREENBERG, S. 5967*
FRIED, M.P. 5790	GLASER, M. 5711	GREGORIO, R.M. 5769
FRIIS, G. 5411	GLAVIND, J. 5514	GRIMELIUS, L. 5945*, 5950*
FRY, R.J.M. 5479	GLAZER, R.I. 5561*	GRINNELL, F. 5687
FUJII, M. 5583*	GLINSKI, W. 5555*	GUILLEMAIN, B. 5667*
FUKUNISHI, R. 5500, 5549*	GNARRA, D.J. 5785	GUINAN, P.D. 5673
FYGE, K. 5911	GCH, S.H. 5485	GUNTHER, G.R. 5990*
GABELMAN, N. 5652	GOLDSTEIN, E. 5907	GUPTA, P.D. 5776
GABRIEL, L. 5890	GOLDSTEIN, N. 5604*	GUSCHIN, B.V. 5653
GAEDICKE, G. 5752*	GOLENETSKII, S.P. 5603*	GUSTAFSON, R.H. 5679
GAETA, J.F. 5938*	GONZALEZ-LAVIN, L. 5852*	GUT, D. 5788
GALJAARD, H. 5600	GOOD, R.A. 5678, 5707	GYENES, L. 5740*
GALLMEIER, W.M. 5454*	GOODMAN, R. 5571*	GYORKEY, F. 5837*
GALLWITZ, D. 5925	GORCZYCA, P.A. 5484	GYORKEY, P. 5837*
GALTON, D.A.G. 5746*	GORDON, S.G. 5973*	HAAPALA, D.K. 5635
GANGOLLI, S.D. 5492	GORMLEY, M.B. 5766	HAAS, H. 5502
GARCEA, R. 5890	GORSKI, A.J. 5707	HACKENBROCK, C.R. 5687
GARCIA, H. 5586*	GOSS, S.G. 5882*	HAKANSON, R. 5950*
GARNER, R.C. 5497	GOTOH, M. 5540*	HAKIMI, M. 5852*
GARRIDO, J. 5929	GOTTLIEB, A.J. 5749*	HALEY, T.J. 5434
GARRISON, A.W. 5869	GOTTLIEB, L.S. 5807*	HAMADA, K. 5470, 5545*
GATTI, R.A. 5683	GOTZ, A. 5650	HAMADA, Y. 5470
GAYLOR, D.W. 5525*	GOUGH, T.A. 5572*	HAMAGUCHI, K. 5738*
GEHRING, P.J. 5467	GRACHEVA, K.P. 5817*	HAMILTON, R.H. 5961*
GEHRKE, C.W. 5975*	GRAFE, A. 5508	HAMMER, H. 5844*
GENTILE, C. 5838*	GRAHAM, F.L. 5660*	HAN, J.C-Y. 5504
GEORGII, A. 5677	GRAHAM, H.M. 5824*	HANCOCK, R.J. 5771
GERICKE, D. 5650	GRAHAM, W.P., III 5963*	HANKINS, J.R. 5820*
GERWIN, B.I. 5629	GRATTAROLA, R. 5594*	HANN, H.W. 5745*
GHELELOVITCH, S. 5843*	GRAY, J.W. 5888	HANN, H.W.L. 5786
GIELKENS, A.L.J. 5630	GRAY, N. 5862	HANSEN, J.A. 5707
GILADI, M. 5907	GRAYZEL, A.I. 5699	HANSEN, M.K. 5781
GILBERT, J. 5464	GREAVES, M.F. 5748*	HARDESTY, B. 5624
GILLAM, J.D. 5868	GREEN, I. 5559*	HARDESTY, B.A. 5896

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HARRER, W.V. 5819*	HILGERS, J. 5633	HYBELS, R. 5847*
HARRIS, C.L. 5635	HILL, M.J. 5865	IAKUBCHIK, T.N. 5931
HARRIS, J.W. 5885	HIROSE, M. 5579*	ICHIHARA, A. 5438
HARRISON, E.A. 5453*	HIROTA, N. 5500	IGLEWSKI, B.H. 5617
HARROLD, J.B. 5662*	HIRT, A. 5899	IGLEWSKI, W.J. 5617
HARVEY, R.G. 5485	HNILICA, L.S. 5915	ILEA, E. 5468
HASHIMOTO, Y. 5537*	HO, H.C. 5428	ILYIN, K.V. 5663*
HASS, B.S. 5544*	HOEL, D.G. 5525*	IMURA, S.-I. 5777
HATANO, T. 5551*	HOFFBRAND, A.V. 5951*	ISA, A.M. 5708
HATCHER, V.B. 5699	HOLDEN, H.T. 5711	ISAKA, H. 5470, 5536*
HATTEN, M.E. 5688	HOLDER, L.E. 5785	ISHIBASHI, Y. 5580*
HATTNER, R.S. 5794	HOLLANDER, C.F. 5606*	ISHIZAKI, R. 5611
HAUDENSCHILD, C. 5949*	HOLLANDER, J.L. 5813*	ISOBE, T. 5738*
HAUSCHKA, T.S. 5570*	HOLLINSHEAD, A.C. 5716	ISOMAA, B. 5930
HAWKINS, D.T. 5442*	HOMMA, K. 5764*	ITANO, T. 5582*
HAWTHORNE, P.K. 5791	HOOGEVEEN, A.T. 5600	IVANKOVIC, S. 5509
HAY-ROE, V. 5604*	HOPKINS, L.N. 5768	IWASHITA, H. 5470
HEADING, C.E. 5492	HORIUCHI, T. 5541*	IYENGAR, M.R. 5972*
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HEIDELBERGER, C. 5481, 5524*	HORWITZ, A.F. 5688	JACOB, F. 5715
HEIJNEKER, H.L. 5660*	HOUSMAN, D.E. 5666*	JACOB, R.J. 5636
HEIMANN, H. 5442*	HOWES, D.T. 5920	JACOBSSON, H. 5928
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HENDERSON, E.E. 5909	HSIA, S. 5658*	JAFFE, N. 5795
HENNING, D. 5976*	HSU, Y.C. 5944*	JAHN, A. 5606*
HERBERMAN, R.B. 5675, 5680, 5700, 5711	HUANG, R.C.C. 5926	JAMRA, M. 5747*, 5761*
HERBST, A.L. 5773, 5814*	HUBBARD, A.W. 5432	JANOWSKI, M. 5664*
HEUER, R. 5982*	HUBER, C. 5743*	JAYARAM, H.N. 5946*, 5947*
HEYWOOD, P.F. 5460*	HUBER, H. 5743*	JEMMALI, M. 5461
HIAI, H. 5651	HUFFMAN, F. 5869	JENSEN, C.E. 5439
HICKOK, D.F. 5712	HUGGINS, C. 5552*	JIRASEK, A. 5670*
HIGGINS, G.A. 5857*	HULTQUIST, G.T. 5945*	JOHANSSON, B. 5941*
HIGGINS, I.T.T. 5430	HUPER, G. 5631	JONES, J.M. 5718

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JUCHAU, M.R. 5548*	KHAITOV, R.M. 5755*	KOHEN, E. 5507
JUHASZ, L. 5876*	KHASIGOV, P.Z. 5987*	KOJIMA, K. 5596
JURET, P. 5910	KHIROYA, R. 5706	KOLAR, G.F. 5506
KAHAN, A. 5844*	KIAVER, H.W. 5514	KOLSCH, E. 5762*
KAHNER, S. 5826*	KIBRICK, S. 5608	KOMENT, R.W. 5639
KAJI, H. 5974*	KIESSLING, R. 5683, 5684	KOMMEDAL, T.M. 5851*
KALLOS, J. 5955*	KIM, B.S. 5644	KONECKI, D. 5896
KALTER, H. 5406	KIM, S. 5922	KOPNIN, B.P. 5519*
KAMALYAN, L.A. 5619	KIM, U. 5734*	KORDAC, V. 5991*
KAMIYA, S. 5584*	KIMBALL, H.R. 5704	KORNHUBER, B. 5650
KANAZAWA, K. 5580*	KIMBLE, C.E. 5484	KORTRIGHT, K. 5646
KANEKO, A. 5720	KIMURA, H. 5954*	KOSHI, K. 5764*
KANO-TANAKA, K. 5581*	KIMURA, S.J. 5632	KOTOMINA, I.P. 5674
KARAKULOV, R.K. 5988*	KIND, J. 5923	KOUNTZ, S.L. 5417
KARASAKI, S. 5475	KING, C.M. 5562*	KRAHN, D.F. 5524*
KARPOV, L.M. 5889	KIRSCHSTEIN, R.L. 5525*	KRAMER, D.L. 5937*
KATSUTA, H. 5916, 5934*	KISTNER, S. 5941*	KRAMER, G.A. 5896
KATZ, D.H. 5451*	KIVINIEMI, K. 5887	KRAUSE, P.H. 5677
KAUR, J. 5746*	KLAGSBRUN, M. 5949*	KRAUSS, E. 5416
KAVANAH, M. 5706	KLAVINS, J.V. 5416	KREBS, A. 5821*
KAWAKAMI, T.G. 5662*	KLEIN, G. 5684	KREHBIEL, J.D. 5966*
KAY, H.E.M. 5786	KLEIN, J.C. 5444*	KRIEG, J.C. 5923
KAY, J.E. 5981*	KLEIN, U.E. 5787	KRIUCHKOVA, G.S. 5817*
KAZANOVA, L.I. 5986*	KLENOW, H. 5957*	KROUSE, T. 5592*
KEARNEY, R. 5681	KLIMA, W.C. 5578*	KROWN, S. 5998*
KEAST, D. 5733*	KLIMENKO, S.M. 5653	KRUEGER, R.G. 5676
KEEHN, R.J. 5857*	KLITSUNOVA, N.V. 5669*	KRUGER, F.W. 5573*
KEELEY, F.X. 5819*	KLUGE, N. 5923	KRUSH, A.J. 5804*
KEHE, C.R. 5885	KMOCH, N. 5502	KUBILUS, J. 5589*
KELLEN, J.A. 5554*	KNIAZEV, P.G. 5614	KULIG, M.J. 5494
KENNEDY, B.M. 5912	KNIZHNIKOV, V.A. 5437	KUPERMAN, O. 5697
KENT, D.R. 5783	KNOWLES, M.E. 5464	KURODA, K. 5539*

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KURTH, R. 5411	LEA, M.A. 5948*	LLOYD, A.G. 5492
KUSHNER, J. 5984*	LECHARPENTIER, D. 5446*	LOBEFALO, G. 5859*
KUZMA, J.F. 5832*	LEDERER, E. 5679	LOGERFO, P. 5832*
KUZNETSOV, O.K. 5614	LEE, B.K. 5980*	LONDON, W.T. 5745*, 5786
KYRKOS, K. 5964*	LEE, C.W. 5965*	LONGFELLOW, D.G. 5980*
LA PLACA, M. 5643	LEFE8VRE, C. 5834*	LOPEZ, C. 5637
LAERUM, O.D. 5558*	LEHMAN, J.M. 5661*	LOPEZ, D.M. 5759*
LAGERCN, A. 5462	LEHMANN, A.R. 5505	LORENZ, R. 5508
LAI, C.-J. 5647	LEINIKKI, P. 5620	LU8BE, I. 5587*
LAING, C.A. 5741*	LEITH, R.S. 5543*	LU88ERT, H. 5495, 5893
LAKE, 8.G. 5492	LELIEVRE, L. 5933*	LUCAS, Z.J. 5697
LAKINGS, D.B. 5975*	LEMON, H.M. 5471	LUDWIG, 8. 5679
LAMENSANS, A. 5679	LEMONNIER, F.J. 5462	LUFTIG, R.8. 5612
LAMERTON, L.F. 5466, 5600	LEONARD, A. 5527*	LURIE, 8.B. 5807*
LAMIE, F. 5633	LEONARD, C.M. 5700	LUST8ADER, E. 5786
LAMON, E.W. 5683	LEPPARD, 8. 5798	LUTTON, J.D. 5907
LAND8ECK, G. 5752*	LESAGE, V. 5530*	LYCKE, E. 5638
LANGARD, S. 5851*	LEVAN, G. 5616	LYMANGROVER, J. 5892
LANGHAM, R.F. 5966*	LEVIN, L.S. 5804*	LYNCH, M.J. 5706
LANGLOIS, A.J. 5611	LEVINE, A.S. 5609	LYNCH, R.G. 5789
LANGNER, A. 5555*	LEVITT, S.H. 5970*	MACHOLDA, F. 5991*
LAPREVOTTE, I. 5659*	LEVY, D. 5667*	MACIAG, T. 5972*
LARSSON, L.-I. 5950*	LEWIS, 8.J. 5973*	MACLENNAN, I.C.M. 5786
LASNERET, J. 5667*	LEWIS, D. 5692	MADSEN, A. 5993*
LASSER, A. 5805*	LI, F.P. 5571*	MADSEN, A.C. 5995*
LATNER, A.L. 5956*	LIDDELL, K. 5767	MAEKAWA, A. 5584*
LAUDEN8ACH, P. 5880*	LIJINSKY, W. 5585*	MAGUIRE, H.C., JR. 5724*
LAUG, W.E. 5521*	LILIS, R. 5442*	MAINS, D.L. 5472
LAUGHLIN, D.C. 5665*	LINDEMANN, M. 5677	MAISIN, J.R. 5664*
LAVOIE, A. 5951*	LINDEN, G. 5527*	MAISKII, V.8. 5817*
LAVRIN, D. 5711	LINDSAY, V.J. 5981*	MAK, T.W. 5666*
LAW, L.W. 5692	LINSELL, C.A. 5870	MAKLER, M. 5962*
LAZARUS, G.S. 5699	LIPKIN, M. 5569*	MALHOTRA, N. 5598
LE, M. 5446*	LIPPMAN, M.E. 5914	MALNASI, ZS. 5844*

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MANNINO, R.J., JR. 5688	MELAMED, M.R. 5782	MIZOGUCHI, H. 5908
MARALDI, N.M. 5643	MELTZER, M.S. 5526*	MIZUTANI, M. 5579*
MARCHETTA, F.C. 5623	MERION, J.A. 5592*	MOCHAN, B. 5972*
MARCOTTE, J. 5547*	MESA-TEJADA, R. 5416	MOCHIZUKI, Y. 5540*
MARGOLET, L. 5691	MEYER, R.R. 5921	MOERTEL, C.G. 5975*
MARKOVIC, L. 5845*	MEYERHOFF, W.L. 5426	MOHR, U. 5465, 5502
MARLAND, P. 5854*	MIADOKOVA, E. 5588*	MOLLER, E. 5401
MARMOR, J.B. 5884*	MICHELITCH, H.J. 5965*	MOLLER, G. 5401
MARSHALL, W.H. 5792	MICHLMAYR, G. 5743*	MOLLER, M.L. 5503
MARTIN, M. 5478	MICKEY, M.R. 5417	MONTESANO, R. 5488
MARTIN, S.E. 5739*	MIKHAILOVA, G.R. 5653	MONTESSORI, G. 5734*
MARTINI, N. 5782	MIKHAL'TSEVICH, G.N. 5931	MONTI-BRAGADIN, C. 5534*
MARUYAMA, K. 5732*	MILISAUSKAS, V. 5719	MOORE, M.A.S. 5942*
MARZ, R. 5952*	MILLER, A.M. 5884*	MORELLI, M. 5979*
MARZLUFF, W.F., JR. 5926	MILLER, L. 5712	MORFIN, R. 5591*
MARZULLI, F.N. 5555*	MILLER, R.G. 5666*	MORI, H. 5500
MASCHIO, F.A. 5503	MILLS, J. 5491	MORI, M. 5550*
MASON, D.Y. 5920	MILLS, L.R. 5472	MORII, S. 5551*
MAURER, U. 5863	MIN, K.-W. 5837*	MORRIS, H.P. 5919, 5922, 5948*
MAZURENKO, N.N. 5655, 5656	MINASE, T. 5720	MORRIS, J.E. 5413
MAZZUCCO, K. 5523*, 5557*	MINEO, T.C. 5716	MORRIS, M.W. 5750*
MCCLAIN, D.A. 5990*	MINOWADA, J. 5623	MORRIS, T.C.M. 5689
MCCLATCHEY, K. 5847*	MINTZ, S.M. 5840*	MORRISON, J.C. 5542*
MCCLOSKEY, J.J. 5813*	MIRABITO, J.A. 5439	MORRISON, W.C. 5542*
MCCOY, J.L. 5692, 5700	MIRAKIAN, A. 5554*	MORTARA, R.H. 5813*
MCLAUGHLIN, J.S. 5820*	MIRONOV, N.M. 5473	MORTON, D.L. 5672
MCNEILL, T.A. 5689	MIRVISH, S.S. 5586*	MOSBAUGH, D.W. 5921
MCWEENY, D.J. 5464	MITARD, M. 5737*	MOSCATELLI, D. 5902
MCWILLIAMS, R.W. 5754*	MITCHELL, T.J. 5463	MOSS, N.S. 5940*
MECHLER, B. 5898	MITELMAN, F. 5423, 5616	MOTTRAM, D.S. 5572*
MEDOFF, G. 5789	MITTELMAN, A. 5570*	MOULE, Y. 5530*
MEHRA, Y.N. 5776	MIURA, Y. 5908	MULDER, C. 5660*
MEIJER, C.J.L.M. 5796	MIYAKAWA, M. 5498	MULLIGAN, R.M. 5522*
MEISSNER, J. 5982*	MIYAMOTO, M.J. 5810*	MURAD, F. 5954*

* INDICATES A PLAIN CITATION WITHOUT ACCOMPANYING ABSTRACT

MURASAKI, G.
5579*
MURGITA, R.A.
5698
MURPHY, G.P.
5938*
MURPHY, J.F.
5835*
MURTHY, T.R.K.
5461
MUSATTI, C.C.
5747*, 5761*
MUTA, K.
5470
MYHR, B.C.
5560*
NADZHARYAN, N.U.
5619
NAGAYO, T.
5774
NAKAI, G.S.
5897
NAKANO, S.
5551*
NAKASHIMA, T.
5815*
NAMBA, Y.
5702
NATHANS, D.
5647
NAVONE, R.
5936*
NAZERIAN, K.
5713
NELSON, D.H.
5822*
NELSON, D.S.
5681
NELSON-REES, W.A.
5791
NERVI, C.
5979*
NETTESHEIM, P.
5463
NEWBERNE, P.M.
5486
NICOLINI, C.
5924
NILSSON, K.
5505
NISHI, M.
5470
NISHIYAMA, H.
5785
NISHIZAWA, K.
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NISSEN, E.D.
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NIXON, J.W.
5980*
NIZZE, J.A.
5672
NOBLE, R.L.
5595*
NOCTER, K.
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NOSE, K.
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NOVAK, J.
5567*
NOYES, A.N.
5691
OBALEK, S.
5555*
OBARA, K.
5512
O'BRIEN, T.G.
5516
ODAKA, T.
5634
ODASHIMA, S.
5584*
OGADA, T.
5879*
OGAWA, K.
5720
OGILVIE, E.J., II
5483
OH, J.O.
5632
OKADA, Y.
5550*
OLDHAM, R.K.
5726*
OLOFSSON, S.
5638
O'LOUGHLIN, S.
5420
OLSSON, L.
5753*
ONG, E.B.
5971*
ONOE, T.
5720
ORTALDO, J.R.
5728*
ORTIZ-MUNIZ, G.
5759*
OSBORN, R.C.
5810*
OSKARSSON, M.K.
5635
OSMANAGIC, I.
5823*
OSTERTAG, W.
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OSTLER, H.8.
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OSTROVSKII, J.M.
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OTA, M.
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OVOMYAN, G.SH.
5657
PAFFENBARGER, R.S., JR.
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PAGE, D.L.
5842*
PAIK, W.K.
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PALESTRO, G.
5936*
PANDHI, S.C.
5776
PANI, 8.
5534*

PAPAC, R.J.
5735*
PARAF, A.
5933*
PARKER, C.M.
5532*
PARKER, J.C., JR.
5813*
PARKER, J.W.
5801*
PARKHOUSE, R.M.E.
5974*
PARKIN, J.
5797
PARODI, A.L.
5667*
PARROTT, D.M.V.
5701
PARSA, K.
5951*
PASCU, L.
5468
PASTOR, K.M.
5501
PASTORE, G.
5878*
PATTERSON, R.L.S.
5572*
PATTERSON, S.W.
5956*
PAULI, G.
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PAULUZI, R.
5979*
PAVIE-FISCHER, J.
5775
PEARLMUTTER, A.F.
5892
PEDIO, G.
5788
PELFRENE, A.
5586*
PERAINO, C.
5479
PERANTONI, A.
5531*
PEREKREST, V.V.
5653
PERETIAT'KO, V.IU.
5900
PEREVOZCHIKOV, A.P.
5614
PERKASH, A.
5962*
PERKINS, P.
5785
PERTSCHUK, L.P.
5766
PETER, H.H.
5775
PETERSON, A.
5569*
PETERSON, C.
5663*
PETRANYI, G.
5684
PETROVA, A.S.
5986*

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PHELPS, B. 5723*	PROBST, G.S. 5921	RHAËSÉ, H.J. 5895
PHILIP, J. 5781	PRODAN, L. 5468	RHIM, J.S. 5559*
PHILLIPS, J.C. 5492	PRUDENTE, R. 5807*	RHODES, D.N. 5572*
PICKERAL, S. 5559*	PRZYBYLSKI, W. 5528*	RIBACCHI, R. 5566*
PIKE, M.C. 5457*	PUCKETT, L. 5894	RICCI, C. 5716
PINPHANICHAKARN, P. 5896	PURCHASE, I.F.H. 5469	RICCIARDI-CATAGNOLI, P. 5664*
PIRAS, M.M. 5913	PURVES, L.R. 5992*	RICCIO, A. 5641
PIRAS, R. 5913	PUSCH, W.M. 5607*	RICE, D.H. 5839*
PISLARU, V. 5468	PUSZTAI, R. 5844*	RICHARDSON, C.R. 5469
PLAISIER, H. 5600	PUTNIK, M. 5845*	RICHART, R.M. 5826*
PLANTEYDT, H.T. 5440*	PYE, E.K. 5972*	RICHMOND, C.R. 5404
PLATA, F. 5414	QIZILBASH, A.H. 5808*	RICHMOND, R. 5725*
PODSTAVKOVA, S. 5588*	QUAGLIANA, J. 5984*	RICKINSON, A.B. 5621
POLAK, L. 5757*	RAAM, S. 5997*	RIJKE, R.P.C. 5600
POLIVODA, B.I. 5905	RACHKEWICH, R.A. 5748*	RINTEL, T.D. 5532*
POLLOW, B. 5495, 5893	RAFIZADEH, B. 5729*	RITTENBERG, M.B. 5617
POLLOW, K. 5495, 5893	RAJ, N.B. 5976*	RITTER, J. 5752*
POORTMAN, J. 5593*	RAMACHANDAR, K. 5723*	RO-CHOI, T.S. 5976*
PORTNOI, L.M. 5817*	RAMO RAO, G.V.S.V. 5763*	ROBBY, S.J. 5773, 5814*
PORTOLANI, M. 5643	RAO, M.S. 5529*	ROBEY, W.G. 5635
POSPELOVA, T.V. 5751*	RAPP, F. 5455*, 5639	ROBINSON, S.H. 5884*
POSTE, G. 5705	RAUSEN, A.R. 5682	RODRIGUES, D. 5675
POT-DEPRUN, J. 5727*	RAVEN, R.W. 5491	ROELANTS, G.E. 5757*
POTTER, M. 5610	RECCHIONE, C. 5594*	ROGERS, A.E. 5486
POTTS, T.V. 5666*	REDDY, J.K. 5529*	ROIZMAN, B. 5636
POUR, P. 5573*	REGAN, J.D. 5585*	ROOTS, R. 5901
POZZI, D.H.B. 5747*, 5761*	REIN, A. 5629	RORHSCHNEIDER, L. 5411
PRAT, M. 5618	REINTOFT, I. 5781	RORSMAN, H. 5911, 5912
PREISLER, H.D. 5907	REISS, J. 5535*	ROSE, F.L. 5497
PREMKUMAR, E. 5610	REMINGTON, J.S. 5694	ROSE, N.R. 5719
PREUSSMANN, R. 5509	RESEGOTTI, L. 5936*	ROSEN, Y. 5766
PRICE, G.B. 5666*	REYNOLDS, R.G. 5484	ROSENGREN, A.M. 5911, 5912
PRICE, M.R. 5710	REZNIK, G. 5489, 5573*	ROSENGREN, E. 5911, 5912
PRIORI, E.S. 5663*	REZNIK-SCHULLER, H. 5465	ROSENKRANTZ, H. 5564*

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ROSENSTRAUS, M. 6000*	SAINT VINCENT, L. 5488	SCHLESIGER, J. 5506
ROSENTHAL, H. 5455*	SAITO, M. 5541*	SCHLOM, J. 5646
ROSLY, I.M. 5987*	SAKABE, H. 5764*	SCHMALL, 8. 5564*
ROSS, 8.D. 5920	SAKAI, K. 5476	SCHMIDT, A.M. 5433
ROSSELET, J.P. 5679	SAKO, K. 5623	SCHMIDT, C.G. 5454*
ROSSET, R. 5461	SAKSELA, E. 5620	SCHMIDT, M. 5678
ROTHENBERG, S.P. 5953*	SALM, R. 5778	SCHMIDTKE, J.R. 5703
ROTTENBERG, V.I. 5856*	SALMON, J.M. 5507	SCHMITZ, R. 5677
ROTTER, V. 5760*	SALSER, J.S. 5520*	SCHNEIDERMAN, M.A. 5525*
ROUBIN, R. 5775	SALYER, D.C. 5784	SCHNUTE, W.C., JR. 5413
ROUNDEHLER, D.P. 5869	SALYER, W.R. 5784, 5842*	SCHOBER, R. 5822*
ROUSSEAU, N. 5530*	SAMROOK, J. 5609	SCHOCHETMAN, G. 5646
ROUYER, M. 5906	SAMER, L. 5534*	SCHOLZ, H. 5487
ROUYER-MUGARD, H. 5906	SAMOJEDNY, A. 5825*	SCHROEDER, T.M. 5422
ROVIN, S. 5848*	SANDERS, 8.R. 5708	SCHWALBE, P. 5787
RUBIN, A.L. 5417	SANDISON, A.G. 5425	SCHWARTZ, A.G. 5531*
RUBIN, H. 5902	SANTISTEBAN, G. 5548*	SCHWARZ, F. 5593*
RUBINSTEIN, L.J. 5822*	SAROFF, J. 5938*	SCHWARZE, E.W. 5787
RUSSELL, C.D. 5780	SASSEN, A. 5664*	SCHWINN, C.P. 5801*
RUSSELL, J.L. 5884*	SATO, C. 5596	SCOTT, P.W.8. 5770
RUSSELL, R.J. 5701	SATO, J. 5538*	SCOTTO, J.M. 5462
RUSSO, I. 5811*	SATO, K. 5919	SCULLY, R.E. 5773, 5814*
RUSSO, J. 5811*	SATO, N. 5512	SECRETO, G. 5594*
RUTTNER, J.R. 5788	SATO, T. 5919	SEGA, E. 5716
RYAN, K.J. 5405	SATTERFIELD, L.C. 5578*	SEGHIR, M. 5880*
RYDEN, A. 5757*	SAVVOV, V.I. 5889	SEHGAL, N.K. 5435
RYTOMAA, T. 5887	SCANDELLA, C. 5688	SELIGMANN, M. 5452*
SABES, W.R. 5848*	SCARPELLI, D.G. 5529*	SELL, S. 5477
SABO, D.L.O. 5985*	SCHACHNER, M. 5717	SENDO, F. 5696
SABY, J. 5811*	SCHAER, J.C. 5863	SENELAR, R. 5756*
SACKMAN, J.W. 5937*	SCHECHTER, R. 5723*	SERROU, 8. 5756*
SADOUGH, N. 5673	SCHENKEIN, I. 5742*	SETLOW, R.B. 5585*
SAFFIOTTI, U. 5459*, 5525*	SCHINDLER, R. 5863	SHABAD, L.M. 5480
SAFFRAN, M. 5892	SCHLEDE, E. 5487	SHACKNEY, S.E. 5436

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SHAIKH, Z.A. 5513	SINGER, P.A. 5610	SPEERS, W.C. 5661*
SHAIN, S. 5455*	SINGER, R.M. 5917	SPENCER, H.J. 5679
SHANMUGARATNAM, K. 5721	SINISCALCHI, C. 5859*	SPIEGELBERG, H.L. 5736*
SHAPOT, V.S. 5473	SIRBASKU, D. 5837*	SPIERS, A.S.D. 5746*
SHARMA, J.M. 5713	SIRSAT, M.V. 5772	SPINA, C.A. 5690
SHARMA, R.P. 5511	SJOBLOM, G. 5930	SPRAGUE, T.H. 5819*
SHARP, P.A. 5609	SJOGREN, H.C. 5710	SPYCHER, M.A. 5788
SHAYMAN, M.A. 5562*	SKAARING, P. 5779	SRIVASTAVA, B.I.S. 5989*
SHEINESS, D. 5894	SKELTON, F.S. 5547*	SRIVASTAVA, P.N. 5598
SHEPHERD, J.H. 5730*	SKLAR, M.D. 5610	STAFFELDT, E. 5479
SHEVACH, E.M. 5559*	SLAGA, T. 5548*	STALKER, D.M. 5921
SHIBATA, H. 5815*	SLESS, F. 5701	STANISLAWSKI, M. 5709, 5737*
SHIBUTA, H. 5580*	SMITH, D.M. 5486	STANLEY, N.F. 5415
SHIELDS, T.W. 5857*	SMITH, E.R. 5564*	STARACE, G. 5979*
SHIMADA, H. 5580*	SMITH, G.H. 5980*	STASIK, L. 5825*
SHIMKIN, M.B. 5565*	SMITH, K.C. 5901	STAVROU, D. 5587*
SHIMOJO, H. 5625	SMITH, L.L. 5494	STAVROVSKAIA, A.A. 5519*
SHIRAI, T. 5579*	SMITH, P. 5457*	STEBLER, M.E. 5839*
SHMEL'KOVA, V.I. 5614	SMITH, W. 5652	STEELE, G., JR. 5710
SHRIKHANDE, S.S. 5772	SMOLENSKAIA, I. 5872	STEFFELAAR, J.W. 5841*
SHUMAK, K.H. 5748*	SNIEGODZKI, J. 5809*	STEFFEN, J. 5450*
SHUMAN, R. 5592*	SOFTIC, DZ. 5823*	STENBACK, F. 5858*
SHURGIN, A. 5477	SOJA, J. 5809*	STENKVIST, B. 5945*
SIEBERS, J.W. 5793	SOKALSKI, W.A. 5983*	STEPAN, J. 5991*
SIEGLER, H.F. 5658*	SOKOLOV, N.A. 5473	STEPANOK, V.V. 5603*
SIEW, S. 5803*	SOKOLOVA, A.N. 5614	STEPHENS, E.A. 5713
SIGEL, M.M. 5615, 5759*	SOLCIA, E. 5950*	STEVENS, L.C. 5969*
SILVA, J.S. 5700	SOLOMON, A. 5410	STEVENS, L.E. 5417
SILVERS, D.N. 5770	SOLOMON, M.P. 5766	STEVENSON, M.M. 5526*
SIMMONS, R.L. 5417, 5703	SONG, C.W. 5970*	STEWART, T.H.M. 5716
SIMONS, M.J. 5721	SONSINO, E. 5854*	STOKER, M.G.P. 5408
SIMSIMAN, R.C. 5516	SONSTEGARD, R. 5965*	STONER, G.D. 5565*
SINCLAIR, T. 5967*	SPATAR ¹ , F.V. 5866	STORER, J.B. 5577*
SINGER, B. 5499	SPECTOR, J.-F.S. 5999*	STRALIN, H.G. 5462

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|--------------------------------|--------------------------------|---------------------------------------|
| STRAUSS, B.
5909 | TEMPLETON, A.C.
5874* | TRUSHINSKAYA, G.N.
5655 |
| STREET, J.C.
5511 | TENG, S.S.
5885 | TSAI, C.
5685 |
| STRUNGE, B.
5806* | TERANISHI, K.
5545* | TSAREVA, A.A.
5653 |
| STUMPF, R.
5762* | TERASAKI, P.I.
5729* | TSUDA, H.
5579* |
| STUTMAN, O.
5968* | TERRACINI, B.
5878* | TSUKADA, H.
5540* |
| SUCIU, I.
5468 | TERRACIO, M.J.
5850* | TURNER, G.A.
5956* |
| SUGAI, S.
5714 | THIEL, E.
5686 | TUTTLE-FULLER, N.
5631 |
| SUGIMURA, T.
5537* | THIERFELDER, S.
5686 | UEMATSU, K.
5552* |
| SUNDARAM, K.
5601 | THIJSEN, J.H.H.
5593* | UEMURA, H.
5512 |
| SUNDLER, F.
5950* | THISSEN, M.R.
5562* | UENO, I.
5541* |
| SUNWOOD, Y.
5790 | THOMAS, R.L.
5404 | UMANSKII, IU.A.
5744* |
| SUSKOV, I.I.
5603* | THOMPSON, B.E.
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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

Carcinogenesis Abstracts is normally published monthly. Volume XIII covers the scientific literature published from Jan 1975 through Dec 1975. To increase the usefulness of *Carcinogenesis Abstracts*, Volume XIII, a Wiswesser Line Notation index and a Chemical Abstracts Service Registry Number index have been provided. These indexes reference compounds described in abstracted articles. A cumulative subject, author, CAS Registry Number, and Wiswesser Line Notation index for Volume XIII will be published shortly after the final regular issue.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations found in *Chemical Abstracts Service Source Index*, 1907-1974 Cumulative, are used. New journals are verified in *New Serial Titles* and abbreviated according to *International Standard ISO 833*. An asterisk indicates the author to address (other than the primary) in requesting reprints.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	Ind.	Indonesian
Ara.	Arabic	Ita.	Italian
Bul.	Bulgarian	Jpn.	Japanese
Chi.	Chinese	Kor.	Korean
Cro.	Croatian	Latv.	Latvian
Cze.	Czech	Lit.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
Eng.	English	Por.	Portuguese
Est.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fle.	Flemish	Ser.	Serbo-Croatian
Fre.	French	Slo.	Slovak
Geo.	Georgian	Spa.	Spanish
Ger.	German	Swe.	Swedish
Gre.	Greek	Tha.	Thai
Heb.	Hebrew	Tur.	Turkish
Hun.	Hungarian	Ukr.	Ukrainian
Ice.	Icelandic	Vie.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

A	angstrom(s)	M	molar
ACTH	adrenocorticotrophic hormone	mM	millimolar
ADP	adenosine diphosphate	μ M	micromolar
AMP	adenosine monophosphate	mOsm	milliosmolar
ATP	adenosine triphosphate	mEq	milliequivalents
BCG	Bacillus Calmette Guérin	min	minute(s)
bid	twice daily	mo	month(s)
C	degrees centigrade	MTD	maximum tolerated dose
cal	calorie(s)	N	normal concentration
kcal	kilocalorie(s)	NAD	nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADH	reduced nicotinamide adenine dinucleotide
CI	curie(s)	NADP	nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NADPH	reduced nicotinamide adenine dinucleotide-phosphate
μ CI	microcurie(s)		
cm	centimeter(s)	ng	nanogram(s) (10^{-9})
CNS	central nervous system	od	once daily
cpm	counts per minute	Pa	ambient pressure
dI	deciliter(s)	PAS	periodic acid-Schiff
ml	milliliter(s)	pg	picogram(s) (10^{-12})
μ l	microliter(s)	pgEq	picogram equivalent
DNA	deoxyribonucleic acid	po	orally
ED ₅₀	median effective dose	ppb	parts per billion
EDTA	ethylenediamine tetraacetic acid	ppm	parts per million
ESR	erythrocyte sedimentation rate	qid	four times daily
g	gram(s)	qod	every other day
kg	kilogram(s)	QO ₂	oxygen quotient
mg	milligram(s)	R	roentgen(s)
μ g	microgram(s)	RBC	red blood cells (erythrocytes)
Hb	hemoglobin	RNA	ribonucleic acid
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
ic	intracerebral	SGOT	serum glutamic-oxalacetic transaminase
icav	intracavitary	SGPT	serum glutamic-pyruvic transaminase
id	intra-dermal	SRBS	sheep red blood cells
ILS	increased life span	TCD	tissue culture dose
im	intramuscular	TCD ₅₀	median tissue culture dose
ip	intra-peritoneal	tid	three times daily
ipl	intra-pleural	U	unit(s)
it	intra-tumorous	mU	milliunit(s)
IU	International Unit	UV	ultraviolet
iv	intravenous	vol	volume
K _m	Michaelis constant	WBC	white blood cells (leukocytes)
LD	lethal dose	wk	week(s)
LD ₅₀	median lethal dose	wt	weight
m	meter(s)	x	times
mm	millimeter(s)	yr	year(s)

REVIEW

- 6001 RAUWOLFIA AND BREAST CANCER. (Eng.)
Anonymous. *Lancet* 2(7929):312-313; 1975.
313; 1975.

Reports suggesting a causal relationship between the use of rauwolfia derivatives and the occurrence of breast cancer are reviewed and evaluated. The initial suggestion of an association between rauwolfia therapy and breast cancer arose from a study of drug therapy immediately preceding 25,000 Boston hospital admissions. Whereas 7.3% of 150 newly diagnosed breast cancer cases had received rauwolfia therapy, only 2.2% of 1,200 age-matched female medical and surgical admissions had received rauwolfia derivatives. Another study has revealed that 1.4% of 708 newly diagnosed breast cancer patients received rauwolfia therapy, as compared to 0.76% of 1,430 female controls with other neoplasms. An additional study has shown that 12.1% of 438 mastectomy patients used reserpine, whereas 7.1% of 438 control patients used the drug. However, later studies have yielded potentially significant variations. Among residents of an affluent retirement community, a risk ratio of 1.2 has been obtained for breast cancer with rauwolfia administration. Similar risk ratios were obtained for an association with hypertension, for any hypertensive drug, for use of any of several groups of drugs, and for attendance at the community clinic. A further comparison showed that 8.0% of 475 women cholelithiasis patients had been hypertensive and had had rauwolfia, vs 6.4% of the 450 breast cancer patients. A study of patients in a state mental hospital revealed that 58% of 55 breast cancer patients and 56% of 55 matched controls had a history of reserpine therapy. The lack of a consistent, specific association between rauwolfia derivatives and breast cancer thus makes a causal relationship appear less likely than was previously supposed. (18 references)

- 6002 VAGINAL ADENOSIS AND OTHER DIETHYLSTILBESTROL-RELATED ABNORMALITIES. (Eng.)
Herbst, A. L. (Harvard Medical Sch., Boston, Mass.); Scully, R. E.; Robboy, S. J. *Clin. Obstet. Gynecol.* 18(3):185-194; 1975.

Existing knowledge regarding clear-cell adenocarcinoma of the vagina and cervix is reviewed with emphasis on its early detection by the examination of diethylstilbestrol-exposed females. The clinical and pathologic features of diethylstilbestrol-associated vaginal adenositis and cervical erosion are also discussed. More than 200 cases of clear-cell adenocarcinoma have been recorded. A definite history of maternal ingestion of stilbestrol, dienestrol, or hexestrol has been substantiated in 65% of the completely investigated cases; in an additional 15% of the cases there is a history of maternal treatment for high-risk pregnancy with an unidentified medication. The development of these cancers does not appear to be dose-related, but the time of initiation of the therapy does seem to be important; in the cancer cases in which the dates of treatment were documented, therapy with the drug was always begun prior to the 18th wk of gestation. In a comparison of the results of examination of a group of

postmenarchal diethylstilbestrol-exposed females with those unexposed controls, several differences were found. Transverse ridges (low fibrous bars in the upper part of the vagina or on the cervix) were seen in 1 of 5 of the exposed females but in none of the controls. There were also differences in the incidence of epithelial abnormalities between the two groups; 35% of the exposed patients had a glandular epithelium (adenosis), while this condition was seen in only 1% of controls. Of the exposed subjects, 95% had areas of the porto vaginalis of the cervix that failed to stain with iodine solution, in comparison to only 49% of the controls. The vaginal adenositis in the exposed subjects was multifocal and consisted of two types of cells: mucinous cells, which resembled endocervical cells; and nonmucinous cells that were often ciliated, resembling those of both endometrial and tubal epithelium. A screening examination and close follow-up of the at-risk population is suggested for early detection of clear-cell adenocarcinoma. Even though direct transition from adenositis to cancer has not been observed, the fact that vaginal adenositis has been found in almost all patients with vaginal adenocarcinoma suggests that it may provide the epithelium of origin for these carcinomas. (14 references)

- 6003 GENETIC TOXICITY OF ENVIRONMENTAL CHEMICALS. (Eng.) Ehrenberg, L. (Wallenberg Lab., Univ. Stockholm, Lilla Frescati, S-104 05 Stockholm, Sweden). *Acta Biol. Jugosl. Ser. B Mikrobiol.* 6(3):367-398; 1974.

The ability of environmental chemicals to induce genotoxic effects (i.e., gene mutation, cancer, teratogenic effects) is discussed. Epidemiological and biological evaluations are described, and viewpoints are given on methods required to decrease the genetic risk of pollutants. A historical review of the discovery of environmental mutagens is presented; it is suggested that 80% of the cancers of the present age are potentially preventable. Genotoxic effects of chemicals are tabulated. A schematic representation of sources of environmental nitrite is presented. It is acknowledged that both major chemical components and impurities may undergo chemical or photochemical reaction or microbial metabolism, giving rise to genotoxic compounds or their metabolic precursors. Studies of the biological aspect and the detection of genetic effects have revealed a linear dose-response curve for even low doses of chemicals, the concept of late effects, and the unspecificity of the agents. The thalidomide catastrophe is cited and the development of a testing organization for the identification of genotoxic chemicals is requested. Various suggested testing methods of the genotoxicity of environmental chemicals include combined *in vitro* and *in vivo* mutagenicity tests, and *in vivo* teratogenicity test, an *in vivo* carcinogenicity test, *in vivo* and *in vitro* chemical tests, and epidemiological survey methods. The quantitative aspect of biological tests is discussed, and a detailed analysis of the resolving power of genotoxicity tests is presented. A tentative genetic risk is assigned; an alkylation of one out of ten million DNA centers, preliminarily characterized as having the nucleophilicity $n = 2.3$ in the

Swain-Scott scale, is associated with the same genetic risk as that of one rad of γ -radiation. Suggested measures to avoid or remove causes of genetic damage involve strict legislative-administrative rules but note the problems involved in testing and evaluating genetic toxicity. Complete reliance on routine testing of suspected chemicals is discouraged, while a cross-scientific and multidisciplinary approach involving levels of administration, evaluation, testing, and research is encouraged. (88 references)

- 6004 A MODEL FOR GASTRIC CANCER EPIDEMIOLOGY. (Eng.) Correa, P. (Louisiana State Univ. Medical Center, 1542 Tulane Avenue, New Orleans, La. 70112); Haenszel, W.; Cuello, C.; Tannenbaum, S.; Archer, M. *Lancet* 2(7924):58-60; 1975.

The hypothesis is presented that one major subtype of gastric carcinoma ("intestinal type") is the end-result of a series of mutations and cell transformation begun in the first decade of life. The mutagen could be a nitroso compound synthesized in the upper gastrointestinal tract by the action of nitrite (i.e., from food or saliva) on naturally occurring nitrogen compounds. Under normal conditions, these nitroso compounds do not reach the gastric epithelial cell, presumably because their synthesis is inhibited by antioxidants present in food or because of their inability to pass the mucous barrier. The barrier may be overcome by abrasives or irritants such as hard grains, food with high NaCl concentration, or surfactants. Once the first mutation occurs, the glandular gastric epithelium is gradually changed to intestinal-type epithelium, the mucous barrier is altered, and the pH is elevated. Under these conditions, bacteria proliferate in the gastric cavity and facilitate the conversion of nitrates to nitrites, thereby increasing the nitrite pool and the probability of formation of mutagenic-carcinogenic nitroso compounds. This process of gastric atrophy and intestinal metaplasia goes on for 30-40 yr until some of the individuals affected have the final mutation or cell transformation that allows the cell to become autonomous and invade other tissues. (15 references)

- 6005 THE EPIDEMIOLOGIC PATHOLOGY OF GASTRIC CARCINOMA. (Eng.) Stemmermann, G. N. (Kuakini Hosp., Honolulu, Hawaii 96817). *Proc. Int. Cancer Congr. 11th.* Vol. 6 (*Tumors of Specific Sites*). Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 242-247.

Studies of the geographic pathology of gastric carcinoma indicate that the presence of intestinal metaplasia is the most likely precursor of this tumor in high-risk populations (e.g., the Japanese). This non-neoplastic state appears in early life (e.g., in 39% of Japanese aged 20-29 yr) and most frequently affects the pyloric antrum. The etiology of metaplasia remains an enigma. A consistently reproducible animal model of this transfor-

mation has not been developed but should be given high priority. Another feature of this tumor which remains to be explained is the distinctive age and sex distribution of its two major types, intestinal and diffuse (the Lauren division). The intestinal type is more frequent in men and older patients and the diffuse form is more common in women and younger patients. There is some evidence that these distribution patterns are the result of host influences upon the morphogenesis of gastric cancer. Possibly these histologic types may be caused by different agents. Several studies suggest that patients with intestinal metaplasia are more likely to develop intestinal gastric cancer, the more common form in high risk areas (rather than the diffuse type. (46 references)

- 6006 FAMILIAL GASTROINTESTINAL CANCER. (Eng.) Hadden, J. W. (Dept. Medicine, Sloan-Kettering Inst., New York, N.Y.). *Clin. Bull.* 5(2): 67-69; 1975.

The possibility of recognizing impending gastrointestinal cancer before the actual onset of malignancy was considered, and evidence for a favorable outcome was summarized. Individuals with a family history of these diseases carry cells with an increased ability to proliferate and accumulate in affected regions before malignancy appears. Abnormal proliferative activity can be detected in predisposed individuals by finding patches of colonic mucosa with abnormal epithelial cells that fail to repress DNA synthesis throughout their life span as they migrate to line crypt surfaces. These patches of abnormal, flat mucosa, appear to be foci for the formation of neoplasms. This type of abnormal cell, unable to repress proliferative activity, is also found in patients with atrophic gastritis, a disease associated with gastric malignancy. However, the persistent DNA synthesis did not in itself indicate the development of malignancy. Similar changes were induced chemically in mice using the compound 1,2-dimethylhydrazine, suggesting that environmental and hereditary factors both have a role in the development of colon cancer. A method of washing cells from the epithelial lining of the colon and incubating them with tritiated thymidine was shown to make possible the detection of abnormal proliferative changes. Further research is underway to develop screening procedures to detect colon cancer at the premalignant stage. (No references)

- 6007 ENVIRONMENTAL MUTAGENESIS: EVOLVING STRATEGIES IN THE U.S.A. (Eng.) Drake, J. W. (Dept. Microbiology, Univ. Illinois, Urbana, Ill. 61801). *Mutat. Res.* 33(1):65-72; 1975.

Environmental mutagenesis is reviewed as to the evolving strategies in the USA. Committee 17, formed by the Environmental Mutagen Society, represents a wide range of genetical specialities and has made recommendations regarding the screening of environmental mutagens and the use of the resulting data. Ideal tests for mutagenicity screening are proposed. The battery of tests employed should be capable of

detecting (with great sensitivity) all types of heritable mutations. The Committee questions human exposure and the extrapolation from test systems to man. The present most potent question is how to conduct risk evaluation, the basic problem being largely quantitative and not merely qualitative. Committee 17 suggests a common unit of mutagenicity, the rem-equivalent-chemical (REC). REC is the dose, or product of the concentration x time, which produces an amount of genetic damage equal to that produced by 1 rem of chronic ionizing radiation in the same test system. The Committee emphasizes specific recommendations about ceiling of exposure to environmental mutagens. The mutagenic limit is set at 5 REC per individual per generation (12.5% increase over the spontaneous human mutation rate). Federal regulatory agencies and their enabling legislation are evolving toward the effective control of this highly complicated problem. (No references)

6008 THE BRITISH EXPERIENCE IN ENVIRONMENTAL MUTAGENESIS: AN EXERCISE IN COLLABORATION. (Eng.) Kilbey, B. J. (Dept. Genetics, Univ. Edinburgh, Edinburgh, Scotland). *Mutat. Res.* 33(1): 73-77; 1975.

The British experience in environmental mutagenesis is reviewed. Tests for mutagenesis are three-fold: the host mediated assay, the dominant lethal test, and *in vivo* cytogenetic tests. These test systems have proven to be insensitive, prohibitively expensive, and time consuming. Four government departments are involved in control of substances entering the environment: the Department of Employment, the Ministry of Agriculture and Fisheries, the Department of Environment, and Department of Health and Social Security. A mutagenicity sub-committee was formed, made up of geneticists and researchers, to advise and make recommendations. The author suggests that tests for mutagenicity should have two basic aims: to determine if a compound or its derivatives are mutagenic *per se* and to estimate the hazards that these agents present to man at the levels of common usage. A very important stage in collaboration between those concerned with governmental control and those concerned with testing will come when the draft lines are released for discussion and comment to industry. (1 reference)

6009 LYMPHORETICULAR MALIGNANCIES AS ENVIRONMENTAL DISORDERS. (Eng.) Vianna, N. J. (Cancer Control Bureau New York State Dept. Health, Albany, N.Y.). In: *Lymphoreticular Malignancies: Epidemiologic and Related Aspects*. Baltimore, University Park Press, 1975, pp. 1-12.

Evidence is presented for lymphoreticular malignancies, including Hodgkin's disease, as environmentally-induced disorders. Geographic epidemiology time-space cluster analysis, migration studies, and evaluation of familial aggregations of a disease were employed to evaluate the importance of the environment in the etiology of lymphoreticular disorders. There were marked differences in the frequency of Hodgkin's disease on an international level and

regionally within certain countries; variations in overall sex and age rates were also noted. In the United States, overall rates were higher than in Japan (from 1950-1953) with a bimodal age-specific curve. Similar curves were observed in Great Britain, Israel, Denmark, the Netherlands, northern Germany, and most all urbanized Western countries. Socio-economic factors were also associated with incidence rates of this disease. Three age patterns for Hodgkin's disease each associated with different levels of economic development were found: (a) developing countries (Peru and Colombia) were characterized by high rates among male children, low rates in the third decade of life and high rates in older age groups; (b) urbanized countries demonstrated low childhood rates, but high rates for young adults and the elderly; and (c) rural areas of developing countries (Puerto Rico) showed high incidence rates among male children, but lower rates for the young adult males than were found for those of urbanized countries. The results of migration studies were also consistent with the theory of environmentally-induced Hodgkin's disease: (a) age-specific mortality rates were higher for Japanese-Americans than for the Japanese, (b) mortality rates for the Israeli were more closely aligned with those of the U.S.'s Caucasian population than for the Japanese, and (c) there was no difference in mortality rates between Caucasians and Japanese living in Hawaii. The results of time-space cluster analysis were variable. A study of 23 familial pairs with Hodgkin's disease revealed a shorter time interval between diagnoses than between age differences of two sibs, suggesting that environmental factors may be more important than genetic factors. Available information from international, regional, and seasonal studies suggests that environmental factors are also important in the etiology of non-Hodgkin's disease. (46 references)

6010 SMOKING AND DISEASE: THE EVIDENCE REVIEWED. (Eng.) Anonymous. *WHO Chron.* 29(10):402-408; 1975.

The correlation between smoking and disease is reviewed based on information presented at the WHO Expert Committee on Smoking, in Geneva, Switzerland, December 1974. A large prospective study shows that Japanese mortality is 22% higher among cigarette smokers (male and female) than among nonsmokers and that the risk increases with increasing number of cigarettes and with inhalation of smoke. The increase in lung cancer in those countries where cigarette smoking is widespread continues without interruption. Filter-tipped cigarettes with low tar do prove less harmful. Smoking cigars and pipes is as dangerous as smoking cigarettes. There is an individual genetic susceptibility to lung cancer that seems to be enhanced by smoking. Lung function in cigarette smokers is impaired in every known respect compared with that of nonsmokers: bronchitis and emphysema are common. Air pollutants seem to increase the liability of lung cancer and obstructive lung disease. Smoking is a major risk factor for both fatal and nonfatal myocardial infarction. Smoking increases ischemic heart disease and the risk of cerebrovascular disease. The incidence of gastro-duodenal ulcers is about twice

as high in smokers as in nonsmokers. Smoking alters the balance between acid and alkaline secretions and disturbs pyloric motility, promoting duodenal-gastric reflux. The main effects of maternal smoking are to retard fetal growth and increase risk of perinatal death. Dependence on nicotine seems to be proven, and withdrawal symptoms contribute to the difficulty in giving up smoking. Exposure of nonsmokers to smokers may cause impaired psychomotor performance, asthma, allergic reactions, and prejudiced cardiac function. The Committee makes several recommendations for the control of smoking suggesting that it is the responsibility of both the government and nongovernmental agencies to create information services, support activities to help people stop smoking, and promote necessary legislation and research. (2 references)

6011 MUTAGENICITY RESEARCH AND TESTING IN SWEDEN. (Eng.) Rameil, C. (Environmental Toxicology Unit, Wallenberg Lab., Univ. Stockholm, Sweden). *Mutat. Res.* 33(1):79-86; 1975.

Mutagenicity research and testing in Sweden is reviewed. There are no legal requirements for mutagenicity testing of any groups of chemicals in Sweden until 1973. However, the genetic risks of chemicals have received wide public recognition. Four chemicals have played a decisive role with respect to legislation: mercury, thalidomide, polychlorinated biphenyls (PCB), and vinyl chloride. Investigations on these products resulted in a new law that requires the manufacturer or seller to furnish the authorities with all the information on the composition and other properties of the product. Mutagenicity testing and screening is done at the university level and is based on a direct interdisciplinary cooperation between chemical and biological divisions. The typical genetic tests used are: 1) single-strand breaks and repair of DNA, 2) back mutations in *Salmonella* with liver microsomes, 3) host-mediated assay, 4) genetic changes in *Drosophila* 5) mammalian bone marrow cells 6) hamster fibroblasts and 7) transformation of human diploid fibroblasts. Results on PCB and vinyl chloride investigations are briefly discussed as examples of projects under joint investigation. There is no conclusive evidence that PCB has mutagenic effects. Of the vinyl chloride derivatives, chloroethylene-oxide is a most potent mutagen. The results indicate that the mutagenic effect of vinyl chloride primarily depends on an epoxidation by liver microsomes. (22 references)

6012 LITTLE MORE ON THE FRYING FRONT. (Eng.) Cooper, P. (No affiliation given). *Food Cosmet. Toxicol.* 13(5):571-572; 1975.

Certain oxidized and heated fats liable to be present in human diets are toxic to experimental animals and may retard growth or induce pathological tissue damage. Experiments demonstrating the adverse effects of feeding animals overheated or oxidized oils are reviewed. In contrast to overheated fats, properly heated fats had a reduced content of carcinogenic polycyclic hydrocarbons and a correspondingly lower tumor-inducing capacity when given to rats in a three-generation feeding study. In another study, a decrease in acetate metabolism in

liver of rats fed heated corn oil (190 C for 132 hr) was reflected in an increased hepatic lipid content, mainly of unsaturated triglycerides. Oxidized oils administered to rats on a vitamin E-deficient diet induced fragility of the membrane of both RBC and liver mitochondria; no RBC hemolysis occurred in animals fed an oxidized oil diet not deficient in vitamin E or a fat-free diet lacking the vitamin. A comparative feeding study showed that cardiac damage, mainly focal myocarditis and fibrosis, was most marked in animals fed corn oil, followed in descending order of myocardial toxicity by cottonseed, soybean and olive oils, beef fat, saturated medium-chain triglycerides, butter oil, chicken fat, and lard. Aeration did not alter the effect of corn oil or medium-chain triglycerides but increased the incidence of myocardial lesions produced by the other fats. Oxidized vegetable fats (but not animal fats) also induced a higher incidence of severe bile-duct proliferation than did the corresponding unoxidized fats. It is suggested that pharmacologically active compounds present in the nontriglyceride fraction of fats, or some unsuspected environmental contaminant, may be markedly altered by aeration and may be responsible for the lesions. (10 references)

6013 HANDLING TOXIC CHEMICALS -- ENVIRONMENTAL CONSIDERATIONS. II. HEALTH HAZARDS TO WORKERS FROM INDUSTRIAL CHEMICALS. (Eng.) Munn, A. (ICI Organics Div., P.O. Box 42, Hexagon House, Blackley, Manchester M9 3DA England). *Chem. Soc. Rev.* 4(1):82-89; 1975.

The role of industrial toxicology in defining health hazards to workers from industrial chemicals is reviewed. Chemicals may enter a workman's body by three routes: ingestion (this route is of little importance in industrial toxicology), absorption through the skin, or absorption by inhalation. Three separate but related matters which are commonly confused are defined and discussed briefly: 1) the toxicity of a compound, 2) the toxic hazard of that compound, and 3) the toxic hazard of an industrial process in which that compound is used. The toxicity of a compound may be measured by animal experiments. The toxic hazard of a compound is only partly a function of its toxicity (as measured by experiment) but also a function of the ease with which it is absorbed into a workman's body. The toxic hazard of an industrial process in which a specific compound is used depends not merely upon the toxic hazard presented by the compound itself, but also upon the circumstances of its use, which determines the extent to which the noxious agent contaminates the environment. Acute industrial poisoning is very rare; most industrial poisoning results from repeated exposures to a toxic agent, with repeated absorption of very small quantities, leading to chronic poisoning. The threshold limit value is the level of atmospheric concentration of potentially hazardous gases, vapors, or dusts, to which it is believed that workers may be exposed 8 hr/day, 5 days/wk, 50 wk/yr, without adverse effects on health or efficiency. The figures represent informed opinion on safe conditions, but do not have

statutory significance in Great Britain. The problems of extrapolating from experiments demonstrating carcinogenic effects in animals to situations involving workmen in industrial conditions indicate that the only assumption that should be made on the basis of such experimental evidence is that a specific compound may represent a hazard. Therefore, all available evidence ought to be critically evaluated both qualitatively and quantitatively. For workmen exposed to small quantities of carcinogens, a "safe" dose can be defined as one which does not bring about a statistically significant increase in tumors, beyond the normal incidence in a population not so exposed. It is concluded that the real question to be considered is not whether a compound is carcinogenic, but whether its manufacture and use presents a carcinogenic hazard to workmen; and, if so, whether adequate precautions can be introduced to obviate that hazard. (No references)

6014 CANCER: HOW CAN CHEMISTS HELP? (Eng.)
Ferguson, L. N. (California State Univ., Los Angeles, Calif. 90032). *J. Chem. Educ.* 52(11): 588-694; 1975.

The potential contribution of chemists to cancer research is discussed. Four major modalities used in cancer treatment are: surgery, radiation therapy, chemotherapy, and immunotherapy. While little is known about the cause of malignant transformation, it is well recognized that chemicals and radiation can produce cancer; the majority of recognized carcinogens or carcinogen precursors consist of polycyclic aromatics, amines, azo dyes, biological alkylating agents, and antibiotics. Miscellaneous carcinogens, of a wide variety of structures, also include aflatoxins, pyrrolizidine alkaloids, and beryllium, arsenic, yttrium, selenium, and cadmium compounds. A discussion of the mechanism of chemical carcinogenesis reveals that the only common feature of the carcinogens is their ease of conversion *in vivo* to strong electrophiles. One mechanism suggests the reaction of the electrophiles with biological nucleophiles; amines are generally hydroxylated *in vivo*, while hydrocarbons are converted to K-region epoxides. In discussing chemotherapy, it is noted that 45 anticancer drugs are currently approved for medical use, ten are in the clinical stage, and 30 are in preclinical testing. These antitumor agents are categorized as alkylating agents, antimetabolites, antibiotics, and miscellaneous. Most drugs currently used inhibit cell division by interfering with the synthesis or use of nucleic acids. Most alkylating drugs are nitrogen mustard, ethylenimines, or alkanesulfonates; these react with the nucleophilic hydroxyl, amine, carboxylate, mercapto, or imidazole groups of proteins and nucleic acids. However, there is little correlation between *in vitro* alkylation activities and cytotoxicity. Antimetabolites are structural analogues taken up but incapable of participating in normal cell metabolism, while antibiotics commonly bind to the RNA molecule. Miscellaneous metal chelates, hindered phenols, and hormonal compounds are also acknowledged. Recent techniques for more effective use of drugs involve combined chemotherapy with sur-

gery and/or radiation therapy, and the co-administration of several drugs. Approaches in the search for potential antitumor agents investigate quantitative structure-activity relationships correlating physicochemical properties with bioactivity and ranking substructure contributions, a target-specific approach, active molecular fragments, and DNA intercalating ability. It is suggested that significant contributions may come from organic, inorganic, physical, clinical analytical, and pharmaceutical chemists, and from biochemists. (76 references)

6015 INDUSTRY, GOVERNMENT SEEK PVC/VCM ANSWERS.
(Eng.) Anonymous. *Rubber World* 171(4):35-57; 1975.

Several aspects of the problem of protecting workers from hazardous exposure to polyvinyl chloride/vinyl chloride monomer (PVC/VCM) are discussed. The necessity of firms to keep in close contact with every regulatory agency in government charged with drafting environmental, health and safety standards is emphasized as is the importance of conferences such as one organized by the Environmental Protection Agency's Office of Toxic Substances which is designed to bring together all concerned parties to present reports and exchange views on the problems associated with atmospheric and effluent discharges by rubber industry firms. Many of the safety systems, embracing monitoring and analyzing instruments, protective masks, and in-plant engineering schemes are also applicable to rubber industry plants and are presented in edited form, including some cost estimates and representative suppliers. Categories of equipment included in this listing are as follows: personal monitoring pumps, gas chromatographs, IR absorption analyzers, colorimetric sensors, and total hydrocarbon or organic vapor analyzers. Other analytical approaches which are listed but not discussed include: a detection system based on the differing physicochemical adsorptive forces of different compounds; an electron-capture detector system; systems based on identifying VCM by its dielectric constant; and an electrolytic-cell gas sensor. Types of respirators which may be used in situations where respiratory protection is required include: air purifying masks, the cartridge types of which are permitted for up to 10 ppm, and the canisters for up to 25 ppm; air-supplied masks, permitted for up to 100 ppm; and self-contained compressed-air bottles. Of all engineering controls applied to the VCM problem, ventilation is probably the most widespread and versatile. Locating exhaust hoods near processing equipment is by far the preferred approach. Proper ventilation is also advisable in warehouses, with cost and airflow requirements possibly being minimized by keeping all PVC segregated. Other factors involved in the design of an efficient exhaust system include the shape of the hood, fan blade configuration, and duct geometry. A list of organizations that can supply services or equipment for monitoring and analyzing for materials that are potentially hazardous to health is included. (No references)

- 6016 ESTIMATION OF THE EFFECTS OF CHEMICAL MUTAGENS: LESSONS FROM RADIATION GENETICS. (Eng.) Wolff, S. (Lab. Radiobiology, Univ. California, San Francisco, Calif. 94143). *Mutat. Res.* 33(1):95-102; 1975.

Lessons from radiation genetics are reviewed to help in the estimation of effects of chemical mutagens. Early studies show that mutations of different types have different responses to radiation. Mutagenic efficiency of the radiation varies with experimental conditions and no unifying data has been available. Point mutations and gross chromosomal mutations are common irradiation effects. Point mutations are insensitive to changes in ion density, whereas chromosomal mutations are induced more efficiently by densely ionizing radiation. Point mutations increase linearly with dose and are independent of the intensity of radiation. A quadratic model for mutation induction predicts values that are very close to most of the observed values. New experiments show that mutation rates are equalized if the data is normalized to the same amount of DNA per nucleus. The implication is that, as evolution proceeds and the amount of DNA in the nucleus increases, the number of genes does not increase but rather the amount of DNA associated with that DNA specifying the structure of proteins becomes greater. This additional DNA may have controlling function and also be mutable so that mutations shut off the gene. If such a relation proves general, it may help extrapolate the effects of chemicals in one organism to another, and to man himself. (21 references)

- 6017 THYROID TUMOR RISK FROM RADIATION DURING CHILDHOOD. (Eng.) Silverman, C. (Div. Biological Effects, Food and Drug Admin., Rockville, Md. 20852); Hoffman, D. A. *Prev. Med.* 4(2):100-105; 1975.

Information about thyroid tumors associated with radiation exposure of the head and neck region during childhood are summarized from seven followup studies and factors to be taken into account in evaluating risks of thyroid neoplasia from such exposures are considered. The seven epidemiological studies include three followup studies of children irradiated for thymic enlargement, two studies of x-ray epilation for tinea capitis, a study of survivors of the atomic bomb in Hiroshima and Nagasaki, Japan, and a followup of those exposed to radioactive fallout in the Marshall Islands. The estimated mean dose to the thyroid gland ranged from 6 to 1225 rad, the period of observation from 16 to 29 yr. A significant excess of malignant tumors of the thyroid was found in all of the studies except in one of the tinea capitis and one of the thymic enlargement studies. In four of the population groups with mean thyroid doses of 229, 20, 143, and 1225 rad, there was consistency in estimated risk: 2.1-2.9 cases/million children/rad/yr. One study of a high-exposure, thymus-irradiated group exposed to 329 rad yielded a cancer risk of 5.5 cases/ 10^6 /rad/yr and in one of the studies of x-ray epilation for tinea capitis, with an estimated thyroid dose of 6.5 rad, a risk figure of 6.1 was

calculated. This unexpectedly low oncogenic thyroid dose directs attention to levels of radiation associated with some diagnostic procedures involving the head and neck region. Estimated adult thyroid doses from four diagnostic x-ray procedures for an "adult reference man" are given as follows: 130 mrad, anteroposterior cervical spine radiograph; 0.5-1.0 mrad, posteroanterior chest plate; 2-12 mrad, two-film dental biting examination; and 30-85 mrad, conventional full mouth dental examination. An uptake test with radioiodines p.o. delivers 6 rad to the adult thyroid with ^{125}I and 10.5 rad with ^{131}I . Scanning procedures with radioiodines p.o. lead to adult thyroid absorbed doses of 2.8 rad with ^{123}I and 100-200 rad with ^{131}I . Thyroid scans with technetium 99-m i.v. deliver about 0.1 rad to the thyroid. Thyroid absorbed doses vary greatly with age, being lowest in adults, progressively higher in children, and perhaps 20 times the adult dose in newborns. It has been reported that ^{131}I beta radiation is less effective than gamma or x-rays in producing cancer at similar levels. These differences have been attributed to several inherent characteristics of the radiations or to the fact that high ablative doses are used which have led to thyroid cell death before malignant changes could develop. It is concluded that evaluation of these findings for applicability to human childhood experience requires further investigation. (25 references)

- 6018 INTRAGENOMAL DISTRIBUTION OF DNA REPAIR SYNTHESIS IN CULTURED HUMAN AND MOUSE CELLS DAMAGED WITH CHEMICAL CARCINOGENS AND ULTRAVIOLET RADIATION. (Eng.) Lieberman, M. W. (Natl. Inst. Environmental Health Sciences, Research Triangle Park, N. C. 27709). *Proc. Int. Cancer Congr.* 11th. Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 149-152.

A series of experiments investigating the intragenomal distribution of DNA repair synthesis and the accuracy of such restoration are reviewed. Employing cultured BALB/c 3T3 mouse cells or human diploid fibroblasts (WI-38), the analyses focussed on the effects of three well-characterized carcinogens and mutagens: UV radiation (254 nm), *N*-acetoxy-2-acetylaminofluorene (NA-AAF), and 7-bromomethylbenz(a)anthracene (7BrMeBA). Analysis of repair synthesis of confluent BALB/c 3T3 cells damaged with UV or NA-AAF has revealed approximately equal repair synthesis in both mainband and satellite DNA. Examination of the distribution of repair synthesis among repetitive and unique sequences in the human diploid genome has noted repair synthesis among sequences of all degrees of repetitiveness, and in approximately the same proportion as their occurrence in the genome. However, the use of high resolution visible light autoradiography has revealed a nonuniform distribution of repair synthesis in WI-38 cells damaged with UVR, NA-AAF, 7BrMeBA, or methylnitrosourea; more repair synthesis occurs in the central portion of the nucleus than in peripheral regions, while the distribution was nonrandom within the

central portion of the nucleus itself. Damage by UVR, NA-AAF, and 7BrMeBA appeared to be repaired by a process involving the removal of about 100 nucleotides in addition to the damaged area; all four deoxyribonucleotides are inserted. The repair patches showed the same thermal elution patterns from hydroxyapatite and resistance to S_1 nuclease as native DNAs; thus 90-95% "of the nucleotides inserted during repair synthesis behave on a double-stranded DNA and appear to be hydrogen bonded to nucleotides on the opposite strand." In addition, analysis of pyrimidine isostich patterns of mouse cells damaged with UVR suggest that repair synthesis is template-directed. A great variety of sequences appear at least partially repairable. Such repair synthesis is template directed and results in an accurate restoration of the damaged area. (24 references)

units, was found in Rous sarcoma virus and in Rauscher leukemia virus virions. The Rous sarcoma virus virion may contain 2-5 reverse transcriptase molecules, against 5-17 in avian myeloblastosis virus virion. Antibodies to the reverse transcriptase inhibit the reverse transcriptase activity *in vitro*. The oncornavirus reverse transcriptase is able to transcribe the entire genome of oncornaviruses into provirus DNA, and also messenger RNAs from other viruses. Nucleotide kinase and nucleotide diphosphate phosphotransferases and nucleoside monophosphate phosphotransferases were also detected in Rous sarcoma virus virions. An enzyme with DNA endonuclease activity, capable of splitting cyclic double-stranded DNA and to transform this DNA from form I into form II was found in Simian Virus SV₄₀ and polyoma virus virions. An enzyme with DNA endonuclease activity, capable of hydrolyzing both DNA chains, was found in adenovirus type 2 and 12 virions. An enzyme with protein kinase activity, phosphorylating the virus structural proteins, was found in virions of herpes simplex virus and equine abortion virus. Further studies will be necessary to elucidate the specific role of virion enzymes in virus replication. It is not known whether these enzymes are coded by the virus or are of cellular origin. (92 references)

- 6019 MUTATING AND MAPPING SV40. (Eng.) Miller, L. K. (No affiliation given); *Nature* 256 (5516):369-370; 1975.

Techniques developed to map the DNA molecule of small mutant simian virus 40 (SV40) genome are described. They are based on the ability of S_1 nuclease to recognize regions of single-stranded DNA and to produce double-stranded cleavages at the mismatched regions. They are ideal for mapping small regions because they are rapid and accurate. S_1 mapping has several advantages over marker rescue; (1) it is accurate to 1% of SV40 genome (55 nucleotides); (2) it is purely biochemical and does not rely on infectivity; and (3) it is useful in mapping nonviral DNA or viral DNA having low ratio of plaque forms/DNA. Caution must be taken that second-site, silent mutations are not mistaken for true mutations. Using appropriate combinations of DNA nucleases it will be possible to produce deletion mutants at restricted nuclear sites and at random sites through the SV40 genome. They will be helpful in differentiating essential regions and limits of various genomes. However, it has been found that certain deletion mutants are not viable, causing problems in obtaining stocks. Stocks of 'helper' viruses will have to be developed that could contribute functions lacking in deletion mutants, yet be easily separable from the deletion mutant itself. It will also be helpful to develop lethal mutants for specific conditions at high frequency. (No references)

- 6021 MAREK'S DISEASE VIRUS, A MODEL FOR ONCOGENIC HERPESVIRUSES--CHEMICAL AND ANTIGENIC PROPERTIES. (Eng.) Biggs, P. M. (Houghton Poultry Res. Station, Houghton, Cambs. PE17 2DA, England). *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 159-165.

The chemical, biological, and antigenic properties of the Marek's disease viruses (MDV) are reviewed, and the use of Marek's disease as a model system for the study of oncogenic herpesviruses and the diseases they cause is described. Isolates of MDV vary greatly in their pathogenicity, ranging from fully pathogenic to completely nonpathogenic. *In vivo* studies employing infectivity tests, immunofluorescence, and nucleic acid hybridization have demonstrated the presence of MDV in cells of most, if not all, organs and tissues of chickens. Infection may be nonproductive, productive but abortive, or fully productive; nucleic acid hybridization and cloning studies strongly suggest that most tumor cells carry several viral genomes. In addition, *in vitro* infectivity experiments show that several types of cells can be infected in culture by either co-cultivation with infected cells or infection with cell free virus. A study of the structural proteins of MDV reveals eight proteins in preparations containing mainly unenveloped virus. Several glycoproteins isolated from infected cells and supernatants of cultured infected cells are also characterized. The DNA of MDV is double stranded, has nonrandom nicks in some of the strands, and has a molecular wt of 1.0×10^8 daltons and an estimated buoyant density of 1.716 gm/cm^3 or 1.706 gm/cm^3 . Immunoprecipitin, immunofluorescence, and immunoferratin

- 6020 VIRION ENZYMES OF VIRUSES IN VERTEBRATES. (Rus.) Gendon, Iu. Z. (Moscow Scientific Res. Inst. of Virus Preparations, Moscow, USSR). *Vopr. Virusol.* (4):387-397; 1975.

Studies on virion enzymes of viruses (picornavirus, togavirus, rhabdovirus, paramyxovirus, orthomyxovirus, oncornavirus, rheovirus, papova virus, adenovirus, herpes virus and pox virus) in vertebrates are reviewed. Over ten enzymes were found in oncornavirus virions. An RNA-dependent DNA-polymerase (reverse transcriptase), capable of synthesizing DNA on virion RNA template resulting in an RNA-DNA hybrid with covalent bonds between the RNA and DNA

tests have been used to study the virus associated antigens of MDV infection. Up to six antigens are noted *via* immunoprecipitation, but only three are regularly recognized; only viruses with the 'A' antigen are capable of spreading. Four morphologically different antigens are described in cultured cells using immunofluorescence; these include a diffuse nuclear antigen, diffuse and granular cytoplasmic antigens, and a membrane antigen. Various immunological procedures show that all strains of the field MDV and herpesvirus of turkeys (HVT) are antigenically closely related. Further studies have suggested that MDV and HVT strains belong to one virus group, and indicate that at least three antigens in addition to the 'A' antigen are associated with each virus strain. Due to the existence of pathogenic and apathogenic field strains of MDV, Marek's disease provides a unique opportunity for the study of herpesvirus oncogenesis; studies of virus/cell relationships *in vivo* and *in vitro* are expected to indicate important differences in the two strains. In addition, immunological studies of MDV function and behavior *in vivo* are expected to suggest a mechanism of oncogenicity of herpesvirus. (47 references)

- 6022 DATA BUILD UP ON CANCER-CAUSING VIRUSES.
(Eng.) Anonymous. *Chem. Eng. News* 53(14): 18-19; 1975.

Evidence from several studies suggesting that viruses passed on genetically from the evolutionary past remain dormant until triggered by some internal or external environmental factor is reviewed. A DNA copy of an RNA type C virus known to cause cancer in the baboon species *Papio cynocephalus* was found to hybridize with DNA extracted from the tissue of healthy baboons of the same species, indicating that the virus was of endogenous origin. The same basic gene sequence found in type C virus was also found in the cells of other Old World monkeys, higher apes, and man. More recently, the baboon type C virus sequences were found in the DNA of cells of domestic cats, suggesting that the primate type C virus infected the cats in the Mediterranean Basin from 3-10 million yr ago. When wild disease-prone mice were crossed with a cancer-resistant strain (B10), the offspring became less susceptible to lymphomas and paralysis, confirming that B10 mice carry at least two regulatory dominant genes which suppress type C virus activity. Certain proteins have been detected in human tissue that are analogous to those proteins produced by RNA cancer viruses; some viral proteins from the baboon, woolly monkey, gibbon, and cat were found in several normal human tissues tested. In other experiments, a type C virus was isolated and grown from the blood of a 61-yr-old woman with acute myelogenous leukemia. Subsequently, the virus was reincubated with fluid from a human embryonic cell culture and on analysis was found to be biochemically and immunologically similar to the viruses known to cause myelogenous leukemia in the gibbon and woolly monkey. The data indicate that the reproducible isolate has been made directly from a human cancer without intervening machinations. (No references)

- 6023 MYELOMA PROTEINS AND CELL DIFFERENTIATION.
(Eng.) Hilschmann, N. (Max-Planck-Institut für experimentelle Medizin, Göttingen, West Germany); Palm, W.; Barnikol, H. U.; Barnikol-Watanabe, S.; Bertram, J.; Horn, J.; Engelhard, M.; Schneider, M.; Dreker, L. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 192-199.

Studies of antibody structure and of genetic mechanisms underlying the cell differentiation processes are reviewed. The high degree of immunoglobulin polymorphism is acknowledged, and the variability of the antigen-binding N-terminal parts (V-parts) of the immunoglobulin molecules is demonstrated. Such variability of the V-parts is due to linked multiple amino acid exchanges and single deletions. Linked amino acid exchanges are also illustrated and compared in the C-part of the K-chains, in λ -chains, and in H-chains. In the V-part, the amino acid exchanges are accumulated in three sections comprising K-chains positions 28-34, 50-56, and 91-96. A schematic model of the V-part of a K-chain REI is presented; the molecule exhibits a high degree of regularity has at least 50% β -pleated sheet structure, and displays hypervariable regions accumulated at one end of the molecule. While the V- and C-part in L-chains are of equal length, the greater length of the H-chain is caused solely by their constant parts. A structural comparison of the constant parts of K-, λ -, γ -, μ -, and parts of the α_1 -chain is presented; the pattern of homology found indicates that all immunoglobulin-chains are derived from a common precursor of about 110 residues by evolution. Chain extension is caused by gene duplication and subsequent fusion; InV- and Gm-factors are inherited as alleles and indicate that the constant sections of each immunoglobulin chain are controlled by one single gene. Hypotheses of the separate genetic control of the V- and C-parts are discussed; subgroup specific exchanges or deletion are interpreted as old mutations while single amino acid changes, are more recent mutations. Comparative sequence analyses of V parts and DNA-RNA hybridization experiments show that the information for antibody specificity is genetically fixed, and indicate a "two-genes-one-polypeptide chain" rule for antibody formation. It is hypothesized that this peculiarity is connected with the differentiation of the antibody forming cells. (24 references)

- 6024 DISTURBANCES IN THE IMMUNE RESPONSE.
(Eng.) Kavetskii, R. (Inst. Oncology Problems, 65 Vasilkovskaya St., Kiev, USSR); Uman'skii, Iu. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 290-294.

Cellular and humoral reactions and disturbances in the immunological mechanism of the host are described. Results of studies on different strains

of mice injected with methylcholanthrene have illustrated that the carcinogen injection with subsequent tumor growth results in a reduction of the number of plaque-forming cells. A similar pattern is found in the studies of cellular immunity factors. A common occurrence in all cases is an activation of cellular reactions at early stages of carcinogenesis followed by inhibition of these reactions at subsequent stages, most markedly in the regional lymph nodes and moderately in peripheral nodes. This cell reactivity insufficiency has also been revealed in the study of other lymphocyte functions, and the immunological reactivity reduction in oncological patients is also marked according to blast-transformation. Tumor development is thus definitely associated with immunodepression. All relevant factors are divided into two groups. The first group of factors includes an insufficient heterogeneity and antigenic complex activity; the second group consists of factors impairing the functions of the connective tissue system, especially the lymphocyte system activity, and includes immunological tolerance and its manifestations. It is suggested that the immune response insufficiency is caused mainly by the state of immunodepression, characterizing the process of tumor growth. The immunodepressive action of most carcinogenic factors of various natures is established and discussed. While the main triggering factor of immunodepression at early stages of carcinogenesis is the carcinogen itself, at subsequent stages, the "antigenic overloading" and antibody influence acting as lymphocyte-blocking agents become increasingly important. It is hypothesized that the tumor process always develops against a background of depression of host (immunological) reactivity. (No references)

6025 AGING AND IMMUNE FUNCTION. (Eng.) Adler, W. H. (Natl. Inst. Aging, Baltimore, Md. 1224). *BioScience* 25(10):652-656; 1975.

Information on normal immune function and information indicative of the existence of age-related immunodeficiency are reviewed. A schema evolved to explain the aberrations seen in immune deficiencies is presented. Under the schema, the primordial immunocyte is a stem cell, capable of differentiating into a class of immunocompetent lymphocytes (T cells) via thymic influence, or into lymphocytes (B cells) via bursa (or bone marrow in mammals) influence. T cells and B cells are further described in functional terms, and a role for cellular immunity as a defense against neoplastic cells is hypothesized. Changes in technical procedures used in studies of cell-mediated immunity (i.e., investigation of T cell function) are described; these include changes in techniques used in delayed hypersensitivity, transplantation, cell culture, lymphocyte cytotoxicity, and lymphokines. The assessment of B cell function is also discussed. Studies of age-associated immune effects investigate possible defects in the stem cell condition, numbers, division potential, and/or differentiation potential. Some studies of stem cell activity show no defect in the number or differentiation of potential of the cells in the aging host;

the results apparently show that stem cells from older immunodeficient mice behave as well as stem cells from young mice when assayed in a young adoptive host, while both perform poorly in an old environment. Examination of various facets of the aging immune system leading to decreased antibody production reveals the general involution of thymic size, the changing morphology of lymphatic tissue, and shifts in the T and B cell populations in spleens from older animals. In studies of humoral immunity, an age-associated decline of primary antibody production is noted, while studies of cellular immunity show ample evidence that T cell function also declines with age. Several theories are presented linking immune function to the causes of aging and the appearance of malignancy. It is thus hypothesized that there may be an association between the function of the immune system, aging phenomena, and age-related disease patterns. (48 references)

6026 PROBLEMS ASSOCIATED WITH STUDY OF CELL-MEDIATED IMMUNITY TO HUMAN TUMORS BY MICROCYTOTOXICITY ASSAYS. (Eng.) Herberman, R. B. (Natl. Cancer Inst., Bethesda, Md. 20014); Oldham, R. K. *J. Natl. Cancer Inst.* 55(4):749-753; 1975.

The problems, including technical aspects, specificity, and relevance, associated with the study of cell-mediated immunity to human tumors by microcytotoxicity assays are described. Technical difficulties included: establishing the base line for calculations of results, the selection of the tissue culture for the target cells, the variations among laboratories in the preparation of effector cells, and the quantitation and reproducibility of results. Regardless of the method used to enumerate target cells remaining at the end of the assay or the attacker:target cell ratios used, considerable differences exist among investigators because of variations in calculations and the expression of results. Good reproducibility was found only when assays were run several days in a row with the same normal individual. The study design of experiments in different laboratories must also be examined in view of the fact that normal human cytotoxic reactivity may be a real phenomenon and that the reactivity of lymphocytes from cancer patients may not be entirely directed against histologic type-specific, tumor-associated antigens. In addition, the possibility of cytotoxic reactivity against individually specific tumor antigens characteristic of carcinogen-induced animal tumors should be evaluated by tests against autologous tumor cells. At present, the authors conclude that microcytotoxicity assays are not suitable for the diagnosis of human cancer or for the reliable monitoring of the course of disease of individual cancer patients. The occurrence of frequent normal reactivity and the consequent difficulties in establishing a constant base line preclude both of these objectives. The authors suggest a concerted effort be made to develop better and more standardized techniques and to carefully analyze any observations made. Thus, it may be possible to utilize cytotoxicity assays as valuable clinical measures of cell-mediated immunity to human tumor-associated antigens. (37 references)

- 6027 DISORDERS OF NEUTROPHIL PROLIFERATION AND CIRCULATION: A PATHOPHYSIOLOGICAL VIEW. (Eng.) Athens, J. W. (No affiliation given). *Clin. Haematol.* 4(3):553-566; 1975.

Disorders of neutrophil proliferation and circulation are reviewed. Some disorders are characterized by elevated blood neutrophil concentration or increased cell production, as in chronic myelocytic leukemia (CML). CML is evidenced by leucocytosis with all stages of granulocytes. Affected patients reveal a higher proportion of blasts, promyelocytes and myelocytes in the marrow. There may be partial but incomplete breakdown in the normal barrier to release immature cells from marrow to blood. CML hence appears as a pre-leukemic state, and true leukemia occurs when the blast crisis develops. The colony stimulating activity (CSA) production may be a manifestation of certain types of leukemia rather than an etiological factor per se. Increased cell production in CML is due to an increased number of Philadelphia chromosome (Ph₁)-positive stem cells with a proliferative advantage over normal stem cells. If unchecked there is a massive accumulation of myeloid cells, with decreased erythrocytes and platelet production and death may result. Polycythemia rubra vera (PVR) is characterized by an increase in RBC mass and blood volume in the absence of tissue hypoxia, accompanied by leucocytosis, thrombocytosis and splenomegaly. Increased survival of labeled cells in the blood and an increase in neutrophil production remains unexplained. Idiopathic myelofibrosis (IMF) may occur secondary to irradiation, toxicosis and infections. Splenomegaly, a leucoerythroblastic blood picture, and hepatomegaly are the result of extramedullary hematopoiesis due to marrow injury. Leukemoid reactions simulate many leukemias including myeloid leukemia. Hereditary neutrophilia is a rare disorder. Acute myeloblastic leukemia seems to correlate with reverse transcriptase activity in marrow cell cultures. Other disorders are characterized by decreased neutrophil concentration and decreased cell production as are congenital aleukia infantile genetic agranulocytosis, cyclic neutropenia, myelokathexis, lazy leukocyte syndrome and other neutropenic states. (68 references)

- 6028 MYELOPROLIFERATIVE DISORDERS (MPD): MYELOFIBROSIS, MYELOSCLEROSIS, EXTRAMEDULLARY HEMATOPOIESIS, UNDIFFERENTIATED MPD, AND HEMORRHAGIC THROMBOCYTHEMIA. (Eng.) Laszlo, J. (Duke Univ. Medical Center, Durham, N. C. 27710). *Semin. Hematol.* 12(4):409-432; 1975.

The spectrum of clinical variants of myeloproliferative disorders (MPD) is discussed, with special emphasis on conditions characterized by primary proliferation of granulocytes, erythroid cells, and megakaryocytes. The various pathophysiological aspects of myelofibrosis, myelosclerosis, extramedullary hematopoiesis, and primary myeloproliferative disorders are presented; a theoretical model consistent with a stimulation of hematopoietic stem cells and fibroblasts in the marrow and depressed extramedullary hematopoietic cells is suggested. Common clinical features of MPD are

described and tentatively correlated with the estimated disease duration. Laboratory features include progressive anemia, massive splenomegaly, granulocyte immaturity, supervening thrombocytopenia, and hyperuricemia. Normal or high leukocyte alkaline phosphatase scores are generally found, as are increased blood and urine histamine levels. Cytogenetic findings show a possible trisomy of C group chromosomes and diverse other abnormalities. Radiologic abnormalities reveal symmetrical osteosclerosis and increased bone blood flow. Patients with undifferentiated MPD or extramedullary hematopoiesis are found equally divided into three types of marrow pathology: marked hyperplasia of erythroid, myeloid and megakaryocytic elements; mixed hyperplasia and fibrosis; and advanced myelofibrosis and myelosclerosis. Methods of treatment may include high doses of androgens, splenectomy, use of the alkylating agents Myleran and Alkeran, radiation therapy, corticosteroid administration, and specific iron or folate replacement therapy. Following a discussion of the background and clinical features of hemorrhagic thrombocythemia, modes of treatment and management are suggested; these involve platelet removal, use of salicylates and dipyridamole, total body radiation, and chemotherapy. A long-range cooperative study of MPD, intended to define the transitions and prognosis of MPD, is outlined. (102 references)

- 6029 HAEMOPOIETIC CELL KINETICS. (Eng.) Schofield, R. (Christie Hosp. and Holt Radium Inst., Manchester M20 9BX U.K.). *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 18-23.

Methods for assaying the hemopoietic stem cell complex, for studying the responses of hemopoietic cell populations to nonequilibrium conditions, and some of the information gathered by these techniques are reviewed. Techniques for making quantitative assessments of parts of the stem cell complex include the spleen colony technique in which pluripotent hemopoietic stem cells are measured by their ability to form colonies in the spleen when injected into heavily-irradiated mice, a method for measuring the relative number of cells capable of responding to erythropoietin by differentiating into hemoglobin-synthesizing cells, and a technique for growing colonies from mouse bone marrow, human bone marrow, and blood from both normal and leukemic subjects in soft agar. Information gathered using techniques to disturb cell equilibrium conditions e.g. ionizing radiation indicates that hemopoiesis may be represented as a three-stage system, of which the best understood branch is erythropoiesis consisting of the following compartments: 1) the pluripotent precursor cell compartment with an extensive capacity for self-maintenance and the ability to give rise, to 2) cells committed to a single line of differentiation, culminating in the erythropoietin-responsive cells, and 3) the maturing compartment of re-

cognizable erythroid cells. The granulocytic series probably consists of similar compartments but no such suggestion can yet be made for the production of platelets. If repeated irradiation is used to deplete the erythropoietic cells of mice, the ability of the stem cells to proliferate declines with each successive irradiation. Grafts of spleen cells showed a similar decline in proliferative ability with successive transfers. A selective elimination of those stem cells with high proliferative capacity was produced by treatment with isopropyl-methane-sulfonate. It is suggested that each time the stem cell population is damaged, even though it may recover well, some of its capacity for recovery has been lost and that repeated treatments that damage this cell population will lead to hemopoietic failure. (45 references)

family resemblance with respect to disease risk is due to nongenetic effects. Studies of dietary habits in connection with risk of colorectal cancer suggest a tentative list of factors whose relationships to colorectal cancer development deserve study: promoting factors - fats, meats, particularly processed meats, and alcoholic beverages; inhibiting factors - vegetarian diet, including such items as fiber, inducers of microsomal enzyme synthesis, and Vitamin A active compounds, and coffee. (21 references)

6031 VASCULAR STRUCTURES IN BRAIN TUMORS.
(Eng.) Hirano, A. (Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, New York, N.Y. 10461); Matsui, T. *Hum. Pathol.* 6(5):611-621; 1975.

The fine-structural appearance of normal brain vasculature is compared with that of brain tumor vasculature. Normal cerebral capillaries have few pinocytotic vesicles and have pentalaminar "tight junctions" between endothelial cells. On the basis of tracer studies, substances that easily cross the endothelial barrier of most other capillaries do not do so in cerebral capillaries. There is a small perivascular space, collagen fibers and fibroblasts are absent, and they are nonfenestrated. Basement membranes of endothelial cells almost abut those of astrocyte vascular processes. Some altered (tumor) vessels are fenestrated and are associated with a wider perivascular space; such vessels are found in pituitary and choroid plexus tumors and in metastatic renal tumors. Pores have also been seen in craniopharyngioma, dysgerminoma and optic nerve glioma near the chiasma; however all of the above types of tissue are or may be served by fenestrated capillaries in the normal state. In some leptomeningeal tumors, in the vascular neoplasms, and in some primary intracerebral tumors and gliomas, fenestrae are also present. Presence of fenestrae in these tumor vessels is considered to be *de novo*, and possibly due to a changed inductive capacity on the part of the tumor cell due to neoplastic transformation. Intracellular junction alterations are difficult to detect because of ethical limitation of tracer studies on humans; however, it is assumed that these junctions are widened. Pinocytotic and coated vesicles are increased in frequency. Large infoldings of the luminal surfaces are also seen. Tubular bodies, rare in normal vessels, are common in certain tumors. In a few tumors, tubular structures which seem to associate with membrane-bound vacuoles within endothelial cells are seen as are tubular arrays between the nuclear membranes and within the cisterns of the rough endoplasmic reticulum. Endothelial proliferation is also a common alteration of tumor vessels. The vessels consist of plump, closely packed endothelium without elongated processes and lumens are often reduced to a slit-like cavity. Intercellular junctions and an abundance of organelles are seen in these cells, which are evidence of cellular immaturity. Filaments, centrioles, and dense bodies are also common. These vascular alterations may be responsible for the edema associated with brain tumors. (54 references)

6030 COLORECTAL CANCER: CLUES FROM EPIDEMIOLOGY. (Eng.) Bjelke, E. (Cancer Registry Norway, Montebello, Oslo 3, Norway). *Proc. Int. Cancer Congr. 11th.* Vol. 6 (*Tumors of Specific Sites*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 324-330.

Epidemiological data suggesting that the major determinants of cancer of the colon and the rectum are exogenous, that these exogenous influences are dependent on constitutional factors, and that nutritional factors play an important role in colorectal cancer development are reviewed. Cancer of the colon and rectum is relatively frequent in North America, Australia and New Zealand and more frequent in most of Western Europe than in South-eastern Europe. It is infrequent in Central America, Africa south of the Sahara, and Asia. With few exceptions, cancer of the colon and the rectum share the same geographic pattern. Incidence rates show an age-pattern of the male/female ratio, which is lowest at 35-55 and has its maximum value after 60. Data on long-term trends in mortality from bowel cancers show differences between countries, between racial and socioeconomic groups within a country, between the sexes and also between the two main sites, colon and rectum. Data for a number of countries show the rate of recognized colorectal cancer to be higher in urban than rural areas. Subjects with ulcerative colitis, Crohn's disease of the large bowel, schistosomiasis japonica, ureterosigmoidostomy and familial polyposis have an increased risk of colorectal cancer. To persons with these rare conditions may be added two larger groups of high-risk persons: those previously treated for large bowel cancer when relatively young, and their close relatives. A continuum of varying degree of dedifferentiation from normal colorectal mucosa over adenomatous polyps to invasive cancer can be demonstrated both morphologically and biochemically, supporting the simplified notion of a continuous distribution of individuals according to their liability to develop colorectal cancer. Familial colorectal studies have shown that it is mainly the younger index patients who show an above-average risk among their relatives. These studies indicate that risk resemblance among sibs is mainly seen among the middle-ages and that part of this

- 6032 STRUCTURE AND FUNCTION OF TUMOR GLYCOPROTEINS. (Eng.) Zito, R. (Regina Elena Inst. Cancer Res., Rome, Italy); Caputo, A.; Floridi, A. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 189-191.

A study of the protein constituents of the ascitic fluid in rats bearing an experimental Yoshida sarcoma, focusing on the α_1 acid glycoprotein, is discussed. Sedimentation and electrophoresis measurements showed a very similar weight and charge for both normal serum and ascites glycoproteins; both glycoproteins were monodispersed, had a sedimentation coefficient of 3.1, an apparent isoelectric point around 2.6, and a molecular wt of 45,000. However, amino acid analyses revealed ten half-cysteine residues in normal glycoprotein but only four in the Yoshida; the tyrosyl content was also lower in the Yoshida glycoprotein. Quantitative pronase digestion of the Yoshida protein moiety yielded a homogeneous glycoprotein. The serum glycoprotein of tumor-bearing animals is very similar in amino acid composition to the ascitic glycoprotein. However, heat denaturation studies by differential spectroscopy have shown a different exposure of the aromatic residues for the two glycoproteins, indicating a conformational difference between normal and Yoshida glycoprotein. Similar to normal glycoprotein, Yoshida glycoprotein is a weak antigen; the tumoral glycoprotein exhibits different and specific antigenicity. The loss of antibody-combining capacity upon the opening of disulfide bonds indicates that the antibody-combining site in both Yoshida and normal serum glycoprotein is composed of residues associated by tertiary structure and remote in sequence. Alkali treatment indicates that the net charge of the molecule plays a minor role in antibody reaction, while immunofluorescence studies have revealed that both Yoshida and normal serum glycoprotein fail to bind to the cell membrane. Whereas direct isolation studies show that normal α_1 glycoprotein is synthesized by the liver, the origin of the Yoshida glycoprotein is not yet known. (5 references)

- 6033 FATTY ACID METABOLISM IN TUMORS. (Eng.) Spector, A. A. (Dept. Biochemistry, Univ. Iowa, Iowa City, Iowa 52242). *Prog. Biochem. Pharmacol.* 10:42-75; 1975.

Available data from studies on fatty acid metabolism in tumors are summarized and compared to data from studies in normal cells. In studies of various transplanted rodent tumors and the Ehrlich ascites carcinoma, it has been found that although fatty acid synthesis from glucose does occur, most of the tumor fatty acid requirements are derived pre-formed from the host animal. Further experiments have demonstrated stimulation of fatty acid biosynthesis by addition of glucose and/or bicarbonate; these experiments have indicated fatty acid desaturation, and have described two fatty acid elongation pathways in various tumors. Tumors have various essential fatty acid requirements. Lack of dietary regulation of fatty

acid biosynthesis has been observed in numerous hepatomas and may be due to an inability of the activators or inhibitors to regulate enzyme or cholesterol synthesis. Studies of glucose incorporation into lipids have indicated major incorporation into the glycerol backbones of lipid esters; indirectly these studies have suggested that most of the incorporated fatty acid is supplied by extracellular sources, i.e., the host. However, additional findings have suggested fatty acid synthesis may play a larger role than presently predicted, and have suggested the occurrence of tumor adaptation to reduced host fatty acid supply via accelerated biosynthesis. Studies on lipids supplied by the host have revealed extreme hyperlipidemia associated with some tumor growth in animals, and have shown reduced tumor growth rate after administration of hypocholesterolemic drugs. Numerous *in vivo* and *in vitro* studies of Ehrlich ascites plasma lipids are cited; comparison of cell and extracellular fluid fatty acid compositions shows that tumor cells obtain a large fraction of their fatty acids and lipoproteins pre-formed from the host. A rapid *in vivo* turnover of ascites plasma free fatty acids has also been found. The regulation of free fatty acid uptake and the oxidation and esterification of free fatty acids by tumor cells are discussed in detail. Esterified fatty acid utilization by tumors has also been observed. Mechanisms of triglyceride uptake are suggested, and phospholipid and glyceride fatty acid turnover is described. Free fatty acid release from Ehrlich tumor cells has been observed. Most studies on fatty acid turnover and utilization have employed Ehrlich ascites carcinoma. Extrapolation of results from one tumor to another may be invalid. (108 references)

- 6034 LIPIDS IN NORMAL AND TUMOR CELLS IN CULTURE. (Eng.) Howard, B. V. (Clinical Res. Center, Philadelphia General Hosp., Philadelphia, Pa. 19104); Howard, W. J. *Prog. Biochem. Pharmacol.* 10:135-166; 1975.

The comparative lipid biochemistry of normal, transformed, and tumor cell lines is presented. Following brief descriptions of the nature of cells in culture and of the distinction between normal and tumor cells, the nutritional requirements of cultured cells are discussed. While some diploid fibroblasts require cholesterol for growth, the requirement for essential fatty acids is not a distinguishing characteristic between the normal and tumor cell types. Data from individual studies of diploid fibroblast lines and established mixoploid lines have shown no striking or consistent differences in the nature of distribution of the major lipid classes. Comparative studies of human, chick, and hamster normal and transformed cells in culture corroborate such findings. Likewise, no differences in the content or distribution of fatty acids have been found between the two cell types; the loss of desaturation ability has been determined not to be a property of tumor cells, but rather a result of prolonged passage in culture. The elevated lipid ethers and decreased α -glycerolphosphate dehydrogenase levels that have been noted are also suggested to be related to the dedifferentiation and adaptation associated with increased (cultured) growth. Studies of lipid metabolism have demonstrated fatty

acid biosynthesis, cholesterol biosynthesis, phospholipid metabolism, and phosphoinositide metabolism in various normal and transformed cell lines; alternative lipid biosynthetic pathways have been suggested from *in vitro* studies of dedifferentiation and adaptation. Further metabolic studies have focused on the regulation of cholesterol biosynthesis, and two regulatory points have been suggested: (a) at the level of β -hydroxy- β -methylglutaryl-CoA reductase, and (b) at a point beyond mevalonic acid. Changes in cell surface properties indicate alterations in the cell surface linked with the neoplastic process; however, virus conversion and the resulting altered cell shape, association, and adhesion is accomplished without any changes in cell membrane lipid biochemistry. Changes in cell transport are correlated with increased phospholipid turnover. Glycolipid and glycoprotein studies have suggested a general pattern of decreased carbohydrate side chain complexity resulting from defective glycosylation in the transformed cells. In addition, studies of lipid uptake by cultured cells have indicated that the rate and amount of lipid flux are dependent on the media protein and lipid concentrations, the density, and the metabolic state of the cells. (153 references)

6035 DEFECTIVE CONTROL OF LIPID BIOSYNTHESIS IN CANCEROUS AND PRECANCEROUS LIVER.

(Eng.) Sabine, J. R. (Dept. Animal Physiology, Waite Agricultural Res. Inst., Univ. Adelaide, Adelaide, S.A., Australia). *Prog. Biochem. Pharmacol.* 10:269-307; 1975.

Studies on the regulation of lipid synthesis and the (defective) physiological control of fatty acid and cholesterol metabolism in cancerous and precancerous liver are reviewed. All of 24 hepatomas tested in four different species (rat, mouse, trout, and man) display defective dietary feedback control of cholesterol synthesis. Similarly, the physiological control of fatty acid synthesis in ten transplanted hepatomas is also insensitive to dietary factors known to grossly alter synthesis in the normal liver. Lipid biosynthesis has also been studied in other tumors and in pretumorous tissue. Experiments employing four diverse chemical hepatocarcinogens (aflatoxin, ethionine, N-2-fluorenylacetylamide, and 3'-methyl-4-dimethylaminoazobenzene) all have shown a breakdown in dietary control of cholesterol synthesis following carcinogen treatment. A discussion of the control mechanisms in normal tissue is presented, and proposed mechanisms of defective controls and possible relationships to the carcinogenic process are reported. Hepatic cholesterol synthesis involves hormone action, feedback control, lasting control, and diurnal rhythm; extracellular, intracellular, and sterol regulators are suggested. β -hydroxy- β -methylglutaryl CoA reductase is presumed to be the rate-controlling enzyme of cholesterol biosynthesis, while the inhibition of fatty acid biosynthesis is assigned to inhibited acetyl CoA carboxylase. Of the three general mechanisms suggested for affecting acetyl CoA carboxylase activity, a hypothesis of feedback inhibition is favored over intracellular long-chain acetyl CoA control or

extracellular hormonal control. Studies of defective controls in hepatomas suggest that the tumors synthesize their sterol requirements predominantly via the same pathway as the liver, and that control breaks down at some point along the route. Defective control of both cholesterol and fatty acid synthesis is thus attributed to impaired production, uptake, or accumulation. Two possible correlative mechanisms of carcinogenesis and defective lipogenesis control relate to functional integrity of the cell and/or a consequential role. The evidence supports the hypothesis that defective control of cholesterol synthesis, and to a lesser extent of fatty acid synthesis, is an integral or essential feature of the carcinogenic process. (185 references)

6036 LARGE BOWEL CANCER: CAUSATION AND MANAGEMENT. (Eng.) McIlmurray, M. B. (City Hosp., Nottingham, England); Langman, M. J. *S. Gut* 16(10):815-820; 1975.

The causes and management of large bowel cancer are reviewed. Comparisons of diets and social characteristics of colonic cancer patients and matched controls have been performed. Proportions of animal protein and fat correlate well with incidence of large bowel cancer: increased fat consumption parallels an increased cancer incidence. Supporting these findings is the correlation between colonic cancer and coronary disease. Animal protein intake is also positively correlated with colonic cancer. An explanation may be that dietary constituents influence the microbial flora of the gut and/or intestinal secretory patterns. The use of carcinoembryonic antigen (CEA) is disappointing in its application as a diagnostic test. The ability for cancer patients to develop an immune response to tumors is studied *in vivo* and *in vitro*. Promising preliminary studies show specific inhibition of adherence after exposing peripheral blood leukocytes from patients with colonic cancer to colonic cancer extracts but this has still to be confirmed on a larger scale. Prospects for improving treatment by nonsurgical means remain vague. Available chemotherapeutic agents are largely ineffective and there is no evidence that adjuvant immunotherapy will be clinically useful. (57 references)

6037 THE CLASSIFICATION AND HISTOGENESIS OF GASTRIC CANCER. (Eng.) Järvi, O. (Dept. Pathological Anatomy, Univ. Turku, Turku, Finland); Nevalainen, T.; Ekfors, T.; Kulatunga, A. *Proc. Int. Cancer Congr. 11th. Vol. 6 (Tumors of Specific Sites)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 228-234.

A classification scheme is proposed for gastric cancer which divides the cancer into two main types: intestinal type adenocarcinoma and diffuse carcinoma. The histogenesis of gastric cancer is reviewed in relation to the classification scheme. Intestinal type adenocarcinoma occurs more often in men and in older age groups than the diffuse type, which is relatively more frequent in younger persons and in women. In the intestinal type, the

metaplastic areas are quite large; in the diffuse type, the metaplastic areas are usually small or even lacking. The intestinal type adenocarcinoma may contain occasional Paneth cells, as well as enterochromaffin cells. Sometimes the secretion of goblet cells is very profuse and a mucinous or colloid carcinoma develops. The highly differentiated Paneth cells and the enterochromaffin cells disappear from the moderately or poorly differentiated adenocarcinomas. The goblet cells are reduced in size and the microvilli of the brush border may be poorly developed. Small intracellular cysts with secretion in the lumen and with microvilli on their wall may develop in some of the tumor cells. These cysts may form a substitute to the goblets as a result of distorted differentiation. On the other hand, obvious, fully developed goblet cells can occur in otherwise poorly differentiated solid carcinomas suggesting the intestinal origin of the tumor. The granules in diffuse type cells resemble more the goblet cell granules than those of the foveolar cells. Intracellular cysts with microvilli similar to those of the intestinal type adenocarcinoma cells were also found in the diffuse carcinoma cells. Mucinous carcinomas occur within the diffuse carcinomas as well as within the intestinal adenocarcinomas. In addition to the two main types of gastric cancer, a third rare type is also discussed: the basic structure in this type is intestinal adenocarcinoma, but glandular buds adjoin the wall of the carcinomatous cavities. Corresponding structures have been seen in the intestinal type tumor of nasal cavities. The classification also includes four other divisions, which are not discussed: 1) squamous cell carcinoma, mucoepidermoid carcinoma, and adenoacanthoma; carcinoid tumor; adenocarcinoma provided with ducts; and others. It is suggested that the intestinal type of adenocarcinoma develops through intestinal metaplasia. A direct malignant change of indifferent foveolar or neck cells is assumed in diffuse carcinoma but in addition, its origin from the metaplastic epithelium is very likely. It is concluded that nearly all malignant epithelial tumors of the stomach bear features of intestinal tumors. (23 references)

6038 THE BIOLOGICAL ASPECTS OF HUMAN HEALTH THREATENED BY AFLATOXINS. (Pol.) Zawirska, B. (50-368 Wrocław, Marcinkowskiego 1, Poland). *Postępy Hig. Med. Dosw.* 29(1):7-24; 1975. (79 references)

6039 MUTAGENICITY TESTING WITH BACTERIA. (Eng.) Rowland, I. R. (No affiliation given). *Food Cosmet. Toxicol.* 13(4):465-467; 1975. (19 references)

6040 TRANSPLACENTAL CHEMICAL CARCINOGENESIS. (Eng.) Napalkov, N. P. (Petrov Res. Inst. Oncology, Leningrad, U.S.S.R.). *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 300-306. (28 references)

6041 DES: ITS USES AND EFFECTS AS CONTRACEPTIVE AND ADDITIVE. (Eng.) Rauscher, F. J., Jr. (Nat'l. Cancer Inst. Bethesda, Md. 20014). *Conn. Med.* 39(7):439-440; 1975. (No references)

6042 THE PATHOGENESIS OF ENDOMETRIAL CARCINOMA. (Eng.) Neves-e-Castro, M. (Reproductive Medicine Study Group, Av. Antonio Augusto de Aguiar, 24 - 2°.dt°. Lisboa 1, Portugal). *Med. Hypotheses* 1(3):135-138; 1975. (71 references)

6043 COLON CANCER AND DIET. (Eng.) Modan, B. (Chaim Sheba Medical Center, Tel Hashomer and Tel Aviv Univ. Medical Sch., Israel); Lubin, F.; Barell, V. *Proc. Int. Cancer Congr. 11th. Vol. 3. (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 272-274. (39 references)

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6068 THE CELL SURFACE AND FIBROBLAST PRO-
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TRENDS. (Eng.) Pardee, A. B. (Moffett Lab.,
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CHEMICAL CARCINOGENESIS

- 6070 ACUTE EFFECTS OF AFLATOXIN B₁ ON tRNA METHYLASE FUNCTION. (Eng.) Busby, W. F., Jr. (Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, Mass. 02139); Hurley, P. M.; Wogan, G. N. *Life Sci.* 17(4):519-522; 1975.

Transfer RNA (tRNA) methylase activity and capacity were measured in relation to the acute effects of aflatoxin B₁ (AFB₁) on rat liver. Weanling male Fischer rats were dosed ip with AFB₁ in amounts corresponding to 1/8, 1/4, and 1/2 the LD₅₀ (0.375, 0.75, and 1.5 mg/kg, respectively). Methylase activities were monitored over a 3-wk period. Methylase activity was elevated approximately 40% within three days after dosing and gradually declined toward control values (approximately 15%) after three weeks. As shown by two-way analysis of variance, the increased tRNA methylase activity in the treated animals was independent of the AFB₁ dose. Gross evidence of hepatic lipid accumulation was apparent in all groups after three days, with relatively little damage noted in the 1/8 LD₅₀ animals. The gross liver appearance gradually returned to normal in all groups except the 1/2 LD₅₀-dosed animals, in which liver size was diminished and ascites were present. Unlike methylase activity, methylase capacity exhibited a linear dose-response relationship, with values for 1/2 LD₅₀-treated animals being approximately 100% higher than control levels at seven days after AFB₁ treatment. The mechanism for the expression of these altered methylase functions is unclear. Either the presence of activators, such as certain polyamines, or the relative absence of inhibitors or competitors would result in elevated methylase function.

- 6071 OXIDATIVE METABOLISM OF AFLATOXIN B₁: OBSERVATIONS ON THE FORMATION OF EPOXIDE-GLUTATHIONE CONJUGATE. (Eng.) Raj, H. G. (Val-labhbhai Patel Chest Inst., Univ. Delhi, Delhi-110007, India); Santhanam, K.; Gupta, R. P.; Venkatasubramanian, T. A. *Chem. Biol. Interact.* 11(4):301-305; 1975.

The formation of an epoxide-glutathione conjugate upon incubation of aflatoxin B₁ (AF B₁) with male albino rat liver preparations was investigated. AF B₁ was prepared by extraction of *Aspergillus parasiticus* cultures with chloroform and purified by thin-layer chromatography. The assay system for the measurement of AF B₁ epoxide glutathione transferase activity consisted of phosphate buffer, 0.1 M, pH 7.4; glucose-6-phosphate, 2 mM; nicotinamide, 2 mM; NADP, 0.2 mM; NADH, 0.2 mM; AF B₁, 0.6 mM; reduced glutathione, 1 mM; glucose-6-phosphate dehydrogenase, 0.6 U; and microsomes equivalent to 1 mg of fresh liver and supernatant (2 ml), in a total volume of 6.0 ml. The results demonstrated the formation of epoxide-glutathione conjugate of the toxin. Enzyme activity was perceptible only with phenobarbital-treated rat (100 mg/kg/day for 3 days) liver preparations. The results imply that glutathione-epoxide transferase activity present in the soluble fraction is induced by pretreating the animals with phenobarbital.

- 6072 INTERACTION OF AFLATOXIN B_{2a} WITH AMINO ACIDS AND PROTEINS. (Eng.) Ashoor, S. H. (Food Res. Inst., Univ. Wisconsin, Madison, Wis. 53706); Chu, F. S. *Biochem. Pharmacol.* 24(19):1799-1805; 1975.

The interaction of aflatoxin B_{2a} (B_{2a}, the hemiacetal of aflatoxin B₁) with amino acids and proteins was studied by spectrophotometric analysis, spectrophotometric titration, equilibrium dialysis, separation of the interaction complex from free reactants by thin layer chromatography (TLC) at pH 7.0, and by the isolation of stable conjugates upon reduction with sodium borohydride. This interaction was demonstrated by all the above techniques. At pH 7.8, the spectrum of B_{2a} (2.1×10^{-5} M) shifted to a longer wavelength (from 370-400 nm) when either glycine (1.3×10^{-4} M) or ovalbumin (2.8×10^{-5} M) was present, but did not shift in the presence of *N*-acetylglycine. Likewise, both glycine and ovalbumin altered the dissociation constant (pK) of the phenolic group of B_{2a}, but *N*-acetylglycine did not. The empirical formula for the complex was B_{2a}(phe)₂ when ¹⁴C-labeled phenylalanine (phe) was used in the interaction. An apparent equilibrium constant for the B_{2a}(phe)₂ system was 1.82×10^7 l. M⁻¹ at pH 7.0. The complex was stable at neutral and slightly alkaline pH but dissociated in acid, contrasting with the reduced adduct which was relatively stable in acidic conditions. The interaction was also pH-dependent with a higher degree of interaction as basicity increased. The results indicate that the alpha- and epsilon-amino groups of amino acids and proteins and the aldehyde groups of the phenolate ion form of B_{2a} were essential for the reaction. The data support the proposed Schiff base formation mechanism for the interaction.

- 6073 ON THE IRRITANT AND COCARCINOGENIC PRINCIPLES OF HIPPOMANE MANCINELLA. (Eng.) Adolf, W. (Institut für Biochemie, Deutsches Krebsforschungszentrum, Heidelberg, Germany); Hecker, E. *Tetrahedron Lett.* (19/20):1587-1590; 1975.

The irritant and cocarcinogenic actions of the manchineel tree (*Hippomane mancinella* L.) were studied. The acetone extract of a methanol preparation of fresh latex from *H. mancinella* was subjected to a procedure yielding an irritant and cocarcinogenic hydrophilic fraction and a non-irritant hydrophobic fraction. Preparative thin-layer chromatography of the hydrophilic fraction yielded a highly irritating mixture M_x of Hippomane factors (M₁, M₂) and a further Hippomane factor (M₃). M₁ and M₂ were not separable by chromatographic means. M₁ was identified as Huratoxin, the tetradeca-2,4-dienoic acid orthoester of a tricyclic diterpene parent alcohol; M₂ was the homologous hexadeca-2,4,6-trienoic acid orthoester of the same parent alcohol. The nonirritant mixture M_x obtained from the hydrophobic fraction represented a mixture of 20-esters of M_x with long chain fatty acid residues representing the typical structures of cryptic irritants and cocarcinogens. M₃ represented a 13-hexadeca-2,4,5-trienoate of 12-deoxy-58-hydroxy-

phorbol-6 α ,7 α -oxide, for which the name "Mancinellin" was suggested. On the mouse ear, the irritant dose 50 (ID₅₀) of M_x was 0.02 μ g, whereas that of M₃ was 0.15-0.20 μ g. It is suggested that the biogenetic precursors of daphnane might be tiglliane type diterpenes.

- 6074 A GENETIC MODEL FOR PATHOGENICITY IN *AGROBACTERIUM* AND FOR TUMOUR INDUCTION IN PLANTS. (Eng.) Kerr, A. (Waite Agricultural Res. Inst., Univ. Adelaide, Glen Osmond, South Australia 5064). *J. Theor. Biol.* 51(2):409-417; 1975.

A genetic model is proposed to explain the pathogenicity of *Agrobacterium* and the transfer of bacterial DNA to plant cells. Two factors have been shown to be highly correlated with pathogenicity in *Agrobacterium*: induction and utilization of the Guanidines octopine and nopaline and sensitivity to bacteriocin 84. On the basis of these observations the authors propose that: 1) the basis of pathogenicity in *Agrobacterium* is the presence of one of two possible transfer factors located on a circular chromosome; bacteria without a transfer factor are nonpathogenic; 2) following conjugation between cells, a transfer factor can transfer DNA from a bacterial cell to a plant cell, or from one bacterial cell to another; 3) the gene for octopine metabolism is located on the chromosome close to one transfer factor and that for nopaline metabolism close to the other transfer factor; and 4) the gene for sensitivity to bacteriocin 84 is located close to the transfer factor for nopaline metabolism. Transfer of virulence as explained by the genetic model involves conjugation between a pathogenic donor bacterium and a nonpathogenic, efficient recipient. Any of the genes or transfer factors may be present or absent in a particular strain which would explain the relevant characteristics of all known strains of *Agrobacterium* with the two possible exceptions of strain A66 and IIBNV6. The author concludes that if the proposed model proves accurate and if conjugation between plant and bacterial cells can be achieved under laboratory conditions, then the process of DNA transfer from bacterium to plant could be interrupted at any stage and thus provide an excellent tool for detailed analysis of the tumor-inducing process.

- 6075 EFFECTS OF SODIUM ARSENITE ON THE SURVIVAL OF UV-IRRADIATED *ESCHERICHIA COLI*: INHIBITION OF A *recA*-DEPENDENT FUNCTION. (Eng.) Rossman, T. (New York Univ. Medical Center, New York, N.Y. 10016); Meyn, M. S.; Troll, W. *Mutat. Res.* 30(2):157-161; 1975.

The ability of arsenite to interfere with the repair UV-induced lesions in *Escherichia coli* was studied. Wild-type and excision-defective strains of *E. coli* B were irradiated with a 15-watt germicidal lamp, as was a *recA* strain. Following UV exposure, serial dilutions were made in phosphate buffer and plated onto nutrient agar containing various levels of sodium arsenite (0-10⁻² M). At concentrations of 0.1 mM and higher, sodium arsenite decreased the survival of UV-irradiated wild-type *E. coli* (a strain which possesses the full complement of repair genes). The effect of the arsenite increased with increasing UV

dose (0-45 sec). Similar results were obtained with the excision repair-deficient strains WWP_a (*uvrA*) and WP6 (*polA*). Sodium arsenite had no effect on the survival of the *recA* mutant WP10. Survival of UV-irradiated WP5 (*exrA*) was enhanced by sodium arsenite particularly at low UV doses. It is postulated that arsenite inhibits a *recA*-dependent step in DNA repair. It accounted for the increased survival of the *exrA* mutant. It is suggested that in the absence of the *exr+* gene, the arsenite-sensitive *recA*-dependent function is deleterious. The ability of arsenite to inhibit DNA repair may account for the clinical and epidemiological reports linking arsenicals with an increased incidence of cancer.

- 6076 THE RELATIONSHIP BETWEEN NITRO GROUP REDUCTION AND THE INTESTINAL MICROFLORA. (Eng.) Wheeler, L. A. (330 Brookline Ave., Boston, Mass. 02215); Soderberg, F. B.; Goldman, P. J. *Pharmacol. Exp. Ther.* 194(1):135-144; 1975.

The capacity of rats to reduce a 25-mg dose of *p*-nitrobenzoic acid (PNBA) was measured by quantifying the amount of this compound recovered in the urine as *p*-aminobenzoic acid (PABA) and its conjugates. Germfree male rats converted approximately 1% of PNBA to PABA; in conventional male Wistar rats the conversion was approximately 25%. Various bacteria isolated from the rat cecum were selectively associated with germfree rats, and it was demonstrated that these bacteria colonized their gastrointestinal tracts. In association with *Lactobacillus plantarum*, the conversion of PNBA to PABA increased to 3.9%. When these rats were further associated with *Clostridium* sp. and *Streptococcus fecalis* the conversion increased to approximately 12%. A general correlation was found between the capacity of constituents of the microflora to reduce PNBA *in vitro* and when associated with the germfree rat. Cecectomy (which removes a substantial portion of the microflora of the rat) decreased the capacity of the six Wistar rats to reduce PNBA (from 22% in intact rats to 7% in cecectomized rats). When two rats of each type were each fed 20 mg *p*-nitrobenzenesulfonamide, the conversion was 5-6% and 46-47% in germfree and Wistar rats, respectively. Thus, this compound is also largely reduced by the flora. Evidence that the reduction of the nitro group in these compounds is carried out by the intestinal microflora explains previous observations in which the reduction of these compounds in rats did not correlate with the activity of liver enzymes putative for these reactions.

- 6077 MACROMOLECULAR COMPLEXES PRODUCED BY 1,3-PROPANESULTONE. (Eng.) Zeldin, P. E. (Univ. Wisconsin Sch. Med., Madison); Bhattacharya, P. K.; Kubinski, H.; Nietert, W. C. *Cancer Res.* 35(6):1445-1452; 1975.

The potential of *in vitro* treatment with 1,3-propanesultone (PS) to induce interactions between nucleic acids was investigated. Nucleic acids labeled with ³²P were extracted from *Escherichia coli* (Q13), *Sarcina lutea*, *Cytophaga johnsonii*, and from Ehrlich

ascites cells. To prevent loss of macromolecules from the acrylamide gel, the gels were covered with a 1-2 mm layer of Sephadex G-25 to act as a trap. PS was added to the nucleic acids in 10^4 - 10^6 M excess. The treatment produced complexes between DNA and DNA, DNA and RNA, RNA and RNA, DNA and proteins and possibly RNA and proteins. PS treatment caused a rapid sedimentation of DNA regardless of length of exposure time and after a constant 30 min exposure. Rapid sedimentation of DNA was observed in alkaline sucrose, indicating that links were stronger than hydrogen bonds. Neither denaturation of DNA nor ionic strength of media affected PS binding. High molecular wt DNA did bind more rapidly. The DNA source also had no effect on PS binding. In association with protein-PS-DNA, there was a density shift from 1.67 g/ml to 1.44 g/ml with a 15-18% protein present in the DNA fraction. The increase in sedimentation of DNA-PS-albumin was no greater than with PS alone. The degree of retention of DNA-PS to nitrocellular filters was related to treatment time and PS concentration. There was an increase in binding of DNA to microsomal membranes at low concentrations of PS (0.1%-0.3%) indicating a change in the DNA-membrane interaction. The influence on RNA was similar, and ribosomal RNA was most susceptible. When excess DNA was added to a PS-RNA complex, the PS effect was enhanced. It is suggested that the PS-nucleic acid complex involves some degree of depurination and interferes with replication chromosome division and transcription.

6078 EFFECT OF A MICROSOMAL SYSTEM ON THE TOXICITY AND INTERACTION OF CERTAIN CARCINOGENIC POLYCYCLIC HYDROCARBONS WITH CULTURED CELLS. (Fre.) Daudel, P. (Fondation Curie-Institut du Radium, 11, rue Pierre et Marie Curie, 75231 Paris Cedex 05, France); Papadopoulos, D.; Markovits, P.; Hubert-Habart, M.; Pichat, L. *C. R. Soc. Biol. (Paris)* 169(3):507-510; 1975.

A liver microsomal system extracted from hamsters pretreated for 1 wk with phenobarbital was added to hamster embryo cell cultures together with a carcinogenic hydrocarbon (7,12-dimethylbenzo(a)anthracene) to study the effects of this treatment on the interaction of the hydrocarbon with the cells, on hydrocarbon toxicity, and on the morphological transformation of the cells and their ability to acquire malignant characteristics. After a 4- or 5-hr treatment (culture medium, tritiated hydrocarbons, and microsomal activation system), the cells were washed and, following digestion, radioactivity was determined by scintillation. The microsomal system significantly facilitated the uptake of the hydrocarbon or its metabolites by the cell; after the 4-hr treatment, the ratio of radioactivities of the material from the experimental cells and that of the controls (no microsomal system) was 1.3 and after 25 hr, was 1.1. In the absence of the microsomal system, only 12% of cells treated with low concentration of hydrocarbon (0.05 μ g/ml) survived; in the presence of the microsomal system and at greater hydrocarbon concentration (0.5 μ g/ml), survival was 32%. Such data could facilitate the study in tissue cultures of metabolites related to A and of their transformation capacity.

6079 CARCINOGENIC ACTION OF 7,12-DIMETHYLBENZO-(a)ANTHRACENE-5,6-OXIDE IN MICE. (Fre.) Chourouloukov, I. (Institut de Recherches Scientifiques sur le Cancer, CNRS, B. P. n° 8, 94800 Villejuif, France); Gentil, A.; Lasne, C. *C. R. Acad. Sci. [D] (Paris)* 281(2/3):207-210; 1975.

The carcinogenicity of 7,12-dimethylbenzo(a)anthracene 5,6-oxide (DMBA-5,6-O) was compared to that of 7,12-dimethylbenzo(a)anthracene (DMBA) in CD 1 mice following im and sc application. Cutaneous treatment consisted of one application of 100 μ g of DMBA-5,6-O or DMBA in 0.1 ml acetone for initiation action. Ten days later, and for 15 months thereafter, the same mice were swabbed three times/wk with 0.005 ml of an acetonetic solution of 0.002% 12-O-tetradecanoylphorbol-13-acetate (TPA, 1 μ g). Carcinogenicity comparison consisted in swabbing two times with 0.05 ml of acetonetic solution of 0.05% of each substance (25 μ g). Each mouse received an sc postero-dorsal injection of 1 mg DMBA-5,6-O or DMBA in 0.1 ml solvent. The carcinogenicity of DMBA-5,6-O was much weaker than that of DMBA; the incidence of tumors was lower, their latency period was longer, the number/animal was reduced to 1, and transformation was weak and late. While there was carcinogenic activity, there was no initiation activity. The incidence of tumors induced in mice initiated with DMBA-5,6-O (47.5%) was the same as that of mice treated with TPA, only (50%); this is not the case when DMBA is used as the initiator. DMBA-5,6-O was hardly active sc, and it did not act on the same cellular type as DMBA; the former induced one angioma and one osteoblastoma while the latter mostly induced fibrosarcomas. The authors suggest that with regard to initiation action, the carcinogenic activity of TPA when it is applied three times/wk may be masking a weak initiation action of DMBA-5,6-O. Region K epoxides of polycyclic hydrocarbons are, with the exception of DMBA-5,6-O, more active *in vitro* (transformation of cultured fibroblasts and mutagenic effects) and less active *in vivo* than related hydrocarbons (DMBA). This could be related to the chemical instability of the epoxides; it is also possible that the region K epoxides are not the active metabolites of the polycyclic hydrocarbons.

6080 DISTURBANCES IN THE HYPOPHYSEAL SEROTONIN LEVELS PROVOKED BY THE ORAL ADMINISTRATION OF A SINGLE DOSE OF 7,12-DIMETHYL-1,2-BENZO(a)ANTHRACENE IN THE RAT. (Fre.) Guerinot, F. (Laboratoire de Biologie Experimentale, Institut Gustave-Roussy, 94800 Villejuif, France); Janiaud, P.; Le Maout, M.; Aubert, C.; Bohuon, C. *C. R. Acad. Sci. [D] (Paris)* 281(2-3):211-214; 1975.

The level of hypophyseal serotonin was studied in female Sprague-Dawley rats after the po administration of a single dose of 7,12-dimethylbenzo(a)anthracene (DMBA), 30-day old rats received 10 mg, 60-day old rats received 25 mg, and 90-day-old rats, 35 mg. Two, five and eight days after administration, the animals were sacrificed and the hypophyses removed. The serotonin level remained low for a significant length of time in the 30- and 60-day-old rats, whereas the level was above average in 90-day-old rats. Since the rate decreased in the medial lobe while it in-

creased in the anterior lobe, a uniquely toxic mechanism of DMBA was excluded. The 60-day-old rats were most carcinogenically sensitive whereas the 90-day-old rats developed very few mammary tumors. The level of serotonin followed a rising curve for 23-60 days. Thus, DMBA affects the level of hypophyseal serotonin. Identical doses given to similar animals following hypophysectomy indicated that the effect of DMBA is the same as that of the ablation of the hypophysis on the level of serotonin. The removal of the gland increased the latency period from 64 to 78 days and decreased the number of tumors/animal from 7.4 to 4.3. The average surface area of the tumors increased from 2.3 to 3.2 cm². Compensation mechanisms existed that restabilized the level of serotonin, but they were blocked when DMBA was administered alone and were active in hypophysectomized animals receiving melatonin daily. In the latter cases, tumor incidence was 100% in controls and 70% in the treated animals. The authors suggest that certain chemical carcinogens may function at the neuro-endocrine level by facilitating proliferation of the mammary parenchyma cells by modifying the hormonal balance through the neuro-amines. The results also reveal the significance of age in facilitating neoplastic proliferation.

- 6081 HIGH-PRESSURE LIQUID CHROMATOGRAPHY OF POLYCYCLIC AROMATIC HYDROCARBONS AND SOME OF THEIR DERIVATIVES. (Eng.) Soedigdo, S. (Coll. Medicine, Univ. Kentucky, Lexington, Kentucky 40506); Angus, W. W.; Flesher, *J. W. *Anal. Biochem.* 67(2): 664-668; 1975.

A technique of high pressure liquid chromatography using three constant solvent compositions to establish the purity and identity of polycyclic hydrocarbons and their derivatives was reported. Benzo(a)pyrene and its derivatives were dissolved in ethanol, ethoxyethanol or ethyl acetate to give a concentration of 1 μ mole/ml and were then injected by means of a microliter syringe directly onto the column. The Permaphase ODS column was eluted with methanol-water mixtures at room temperature. Retention times were measured at a flow rate of 1.5 ml/min. Methanol: water, 75:25, was a convenient eluant for most of the compounds studied, giving short retention times and sharp peaks. The change of composition of the eluant from 75:25 methanol:water to 65:35 changed the retention time of most compounds by a factor of about two, facilitating differentiation between the compounds. Retention times greater than 15 min were not desirable for a rapid analytical method. While the gradient method is probably the best suited for examining complex mixtures of derivatives, the isocratic method seems more suitable for establishing the identity of two samples that are presumed to be the same compound.

- 6082 ASSAY AND PROPERTIES OF GLUTATHIONE-S-BENZO(a)PYRENE-4,5-OXIDE TRANSFERASE. (Eng.) Nemoto, N. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Gelboin, H. *Arch. Biochem. Biophys.* 170(2):739-742; 1975.

An assay for glutathione-S-benzo(a)pyrene-4,5-oxide transferase is described, and some of the proper-

ties of this enzyme are discussed. Filtered liver homogenates were centrifuged at 10,000g for ten minutes. The upper 2/3 of supernatant was centrifuged at 105,000g for 60 min and incubated with 0.5 mM reduced glutathione and 5×10^{-5} to 10×10^{-5} M [³H]benzo(a)pyrene catalyzed the formation of a conjugate of glutathione and [³H]benzo(a)pyrene-4,5-oxide. The conjugate was isolated by thin-layer chromatography and identified by its radioactivity and its ninhydrin reactivity. When both [³H]benzo(a)pyrene-4,5-oxide and [¹⁴C]glutathione were used, the radioactivity from each precursor was in the conjugate. The reaction was linear, with protein concentration from 10-400 μ g protein. Transferase activity was pH-dependent and sensitive to heat and pronase digestion. The amount of nonenzymatic conjugation was negligible under all the conditions described. This procedure measures a key enzyme in polycyclic hydrocarbon metabolism; its activity may relate to the efficiency of detoxification of active carcinogenic intermediates.

- 6083 INDUCTION OF ARYL HYDROCARBON (BENZO[a]-PYRENE) HYDROXYLASE IN FISH BY PETROLEUM. (Eng.) Payne, J. F. (Environment Canada Fisheries and Marine Service Biological Station, Water St. East St. John's, Newfoundland, Canada, A1C 1A1); Penrose, W. R. *Bull. Environ. Contam. Toxicol.* 14(1):112-116; 1975.

The effect of environmental petroleum contaminants on aryl hydrocarbon hydroxylase (AHH) activity of several species of fish was investigated. Brown trout (*Salmo trutta*) 2-4 yr old were collected from an uncontaminated lake, and from an oil-polluted lake. Capelin (*Mallotus villosus*) 2-4 yr old were captured at the seashore during spawning. In all AHH measurements, liver and gills were removed from freshly killed fish. Homogenates were centrifuged, and the supernatants were assayed for aryl hydrocarbon [benzo(a)pyrene] hydroxylase activity and protein content. In *in vivo* induction experiments, significant increases in the specific activity of liver AHH were found in both trout and capelin. There was no significant increase in gill AHH activity, and no noticeable differences in mortality or behavior. Specific activities of liver AHH of trout from the clean and polluted lakes were significantly different (26.5 ± 19.4 vs 362 ± 51 U/mg protein), indicating that environmental factors were reflected in the enzyme levels. Although it was acknowledged that AHH may not be specifically induced by oil, it is suggested that the amount of aryl hydrocarbon[benzo(a)pyrene] hydroxylase activity may serve as a useful index of recent or long-term oil exposure in fish.

- 6084 SIMPLE VS. COMPLEX INHERITANCE OF INDUCIBLE ARYL HYDROCARBON HYDROXYLASE IN MOUSE TISSUES. (Eng.) Burki, K. (Medical College of Georgia, Augusta, Ga.); Liebelt, A. G.; Brennick, E.* *Biochem. Genet.* 13(7/8):417-433; 1975.

The genetics of induction of hepatic and lung aryl hydrocarbon hydroxylase (AHH) were studied in Af/Ki and AKR/Ki mice and in their F₁ and F₂ progeny after administration of 3-methylcholanthrene (3MC). Furthermore, the induction of AHH was investigated

using the fetal liver explant model system with 3MC, trans-1,2-dihydroxy-3MC, and 4'-bromoflavone as the inducers. The results obtained with the above strains were contrasted with those from the C57BL/6K1, DBA/2⁺K1, and their crosses. This investigation revealed a complex pattern of inheritance of basal and inducible AHH in lung and liver of AKR/K1 and Af/K1, with a poor correlation between lung and liver. Hepatic AHH was not fully inducible in the F₁ hybrids, while the frequency distribution function in the F₂ mice was suggestive of more than two distinct classes.

- 6085 BENZO(a)PYRENE-4,5-OXIDE HYDRATASE: ASSAY, PROPERTIES, AND INDUCTION. (Eng.) Leutz, J. C. (Natl. Cancer Inst., Bethesda, Md. 20014); Gelboin, H. V. *Arch. Biochem. Biophys.* 168(2):722-725; 1975.

The properties and induction of benzo(a)pyrene-4,5-oxide (BP-4,5-oxide hydratase), and a simple and rapid assay for the hydratase activity, are described. Uniformly tritium-labeled BP-4,5-oxide of specific activity 304 mCi/M was synthesized. Liver microsomes were prepared from male Sprague-Dawley rats of 150-200 g. The assay mixture consisted of glycine-NaOH buffer, rat liver microsomal protein, and BP-4,5-oxide in methanol. A single product, benzo(a)pyrene-4,5-dihydrodiol, was identified by comparison spectroscopy. The disappearance of the BP-4,5-oxide showed a near stoichiometric relation to the formation of product, which was proportional to the protein concentration range tested. In five preparations tested, the hydratase showed a 30- to 400-fold greater activity than the benzo(a)pyrene hydroxylase. The hydratase had no requirement for NADPH or Mg²⁺, was insensitive to EDTA, and was inhibited by 1,1,1-trichloropropylene oxide (0.17 nM/min/mg). In addition, it was resistant to digestion by trypsin and pronase. However, after detergent treatment, the hydratase became completely inactivated by pronase digestion. While phenobarbital (15 nM/min/mg) increased both hydratase and aryl hydrocarbon (benzo(a)pyrene) hydroxylase activity, methylcholanthrene (5 nM/min/mg) pretreatment increased only hydroxylase activity. The assay indicates inactivation of the K-region of BP-4,5-oxide. Hence, the results suggest the ratio of hydratase to coupled mixed-function oxygenase may be significant in the detoxification of metabolites.

- 6086 FINE STRUCTURAL CHANGES INDUCED IN RAT HEPATOCYTES BY SINGLE DOSES OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE. (Eng.) Flaks, B. (Univ. Bristol, Medical Sch., Bristol, Great Britain); Teh, E.-C. *Chem. Biol. Interact.* 11(4):277-289; 1975.

The hepatic cell changes induced by a single dose of 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) were studied in rats, with particular attention to the pathogenesis of the unusual clear cytoplasmic areas that are associated with these cell changes. Male Leeds rats were given single po doses of 150 or 300 mg/kg of 3'-MeDAB. They were sacrificed 24 or 48 hr after treatment, and their hepatic tissues were examined by electron microscopy. The development was observed of an unusual cytoplasmic change, which consisted of large perinuclear areas of decreased

hyaloplasmic density, devoid of glycogen or organized structures, which displaced the organelles to the cell periphery. This arose by the formation of large glycogen lakes, which coalesced and then lost their glycogen content, and this was accompanied by nuclear irregularity and shrinkage. Other changes, affecting the endoplasmic reticulum and the cell surface, appeared to be similar to those induced by chronic azo dye feeding. It was concluded that the acute lesion observed may limit any specific responses of the hepatocytes to the presence of 3'-MeDAB.

- 6087 INHIBITED INITIAL RATES OF POLY-URIDYLIC ACID-DIRECTED PHENYLALANINE INCORPORATION BY FREE RIBOSOMES FROM THE LIVER OF RATS FED HEPATOCARCINOGENS. (Eng.) Kizer, D. E. (Biomed. Div., Samuel Roberts Noble Found., Inc., Ardmore, Okla.); Clouse, J. A. *Biochem. Pharmacol.* 24(9):1019-1023; 1975.

The effect of hepatocarcinogens fed to rats on *in vitro* protein synthesis by ribosomes from the liver was studied. Female Holtzman rats were fed diets containing 3'-methyl-4-dimethyl-aminoazobenzene for four weeks; control rats were fed the basal diet. Free ribosomes and membrane-bound ribosomes were isolated from rat liver tissue and the initial rates of phenylalanine incorporation into proteins were determined both in the absence and presence of poly-uridylic acid. When the results from two groups of animals were compared, only the free ribosome systems showed a significant difference in the initial rates of protein synthesis. The presence of poly-uridylic acid did not change the rate of incorporation for ribosomes from rats fed the hepatocarcinogen; however, it stimulated the rates for ribosomes from the control group. The inhibition of phenylalanine incorporation in rats fed 3'-methyl-4-dimethyl-aminoazobenzene was reversible and was not associated with defective binding of poly-uridylic acid. Similar effects on the free hepatic ribosomal populations were found in rats of other species and sex. The authors conclude that the ribosomal entity of the protein biosynthetic mechanism was affected by the hepatocarcinogens and suggest that this change may be correlated with the animals' risk for cancer.

- 6088 SPECIES DIFFERENCES IN BENZENE HYDROXYLATION TO PHENOL BY PULMONARY AND HEPATIC MICROSOMES. (Eng.) Harper, C. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, N.C. 27709); Drew, R. T.; Fouts, J. R. *Drug Metab. Dispos.* 3(5):381-388; 1975.

The metabolism of benzene to phenol by microsomal preparations from lung and liver was compared in female Syrian hamsters, female Sprague-Dawley rats, and male New Zealand White rabbits. Lung and liver homogenates were centrifuged at 10,000 x g. The assay mixture for benzene metabolism contained 11.2 mM [U-¹⁴C]benzene and 2.5 mg microsomal protein; the mixture for phenol metabolism contained 2.5 M-[U-¹⁴C]phenol and 2.5 mg protein. The products of benzene metabolism were extracted with ethyl acetate and analyzed by gas-liquid chromatography.

The differences in K_m values between the three species were small, but in a few cases, they were statistically significant (hamster lung was 3.09 mM, while rat and rabbit were 4.86 and 10.04, respectively, $p < 0.05$). The maximum velocity differed widely among species and tissues. The V_{max} differed in the following order: rabbit lung = hamster liver > rabbit liver > hamster lung > rat liver = rat lung. Benzene could inhibit its own metabolism *in vitro* when present in high concentrations. Phenol was the only metabolite of benzene identified, under the conditions of the assay, in incubation mixtures containing microsomes from lung or liver of any of the three animal species. When incubated with microsomes under the conditions used to measure benzene metabolism, phenol was further metabolized in liver but not in lung preparations. Phenol metabolism was almost completely inhibited when 11.2 mM benzene was included in the incubation mixture containing hepatic microsomes. The variation in rates of benzene hydroxylation by microsomal preparations from lungs or livers of the three animal species was similar to the variation in rates of benzyrene hydroxylation in the same preparations. The relative importance of liver *vs* lung hydroxylation of benzene to phenol was demonstrated by the ratios of liver to lung rates of benzene hydroxylation; these were 38.4, 32.4, and 8.8 for hamster, rat, and rabbit, respectively. The liver is thus more important than the lung for total body clearance of benzene. Lung metabolism is probably more important in preventing the accumulation of benzene in the lung than in contributing to the total body metabolism of benzene.

- 6089 CARCINOGENESIS FROM POLYURETHANS. (Eng.) Autian, J. (Univ. Tennessee Cent. Health Sci., Memphis); Singh, A. R.; Turner, J. E.; Hung, G. W. C.; Nunez, L. J.; Lawrence, W. H. *Cancer Res.* 35(6):1591-1596; 1975.

Seventeen polyurethans, containing various monomeric structural units, and a polyethylene were implanted ip in groups of male black Bethesda rats; 13 of the polyurethans and the polyethylene were also implanted in females. Tumorigenesis of each material was evaluated for up to two years. Tumor development in these animals was expressed in terms of the incidence in the at-risk population, and the tumorigenic latent period was approximated for each sample. Twenty months after implantation, the relative tumorigenicity (area under the corrected cumulative tumor mortality *versus* time curve) in the males ranged from zero (for the unimplanted controls) to 6.18 (for polyurethan Y-238); for female rats this range was 0.29 (for unimplanted controls) to 5.72 (for Y-238). Estimated latent periods in the males ranged from 5-8 mo (for Y-304 and Y-303, respectively), and 22.5 mo for the unimplanted controls; for the females, the range was from 8-13.5 mo (for Y-290 and Y-217, respectively), and 14 mo for the unimplanted controls. The relative tumorigenicity of each sample was also compared to its *in vitro* activation energy for thermal decomposition. The results show an increased incidence of fibrosarcomas in rats given implants. Although the experiment was designed to avoid tumor formation *via* the solid-state mechanism

(as opposed to the chemical mechanism), solid-state carcinogenesis cannot be ruled out completely.

- 6090 LACK OF EFFECT OF BLOOD SAMPLING-INDUCED HAEMATOPOIESIS ON *IN VIVO* CHROMOSOME DAMAGE BY CYCLOHEXYLAMINE IN CHINESE HAMSTERS. (Eng.) van Went-de Vries, G. F. (Lab. Pharmacology, Natl. Inst. Public Health, P. O. Box 1, Bilthoven, The Netherlands); Kragten, M. C. T.; van den Bosch, R. A. *Food Cosmet. Toxicol.* 13(4):419-421; 1975.

Experiments were conducted to determine the effect of reactive hematopoiesis on chromosome damage induced by cyclohexylamine. Chromosomes of 12 Chinese hamster lymphocytes were analyzed before and after po administration of cyclohexylamine (200 mg/kg, for three days) and before and after reactive hematopoiesis. Twelve other hamsters were left untreated. The reactive hematopoiesis was induced in both groups by the taking of the relatively large sample of blood necessary for lymphocyte cultures. No increase in chromosome aberrations was found in the cultures prepared after the production of new blood cells. Cyclohexylamine, however, induced a significant increase in structural chromosome abnormalities. It appears that hematopoiesis has no effect on chromosome aberrations caused by cyclohexylamine.

- 6091 3-METHYLCHOLANTHRENE UPTAKE AND METABOLISM IN ORGAN CULTURE. (Eng.) Lasnitzki, I. (Strangeways Res. Lab., Cambridge, England); Bard, D. R.; Franklin, H. R. *Br. J. Cancer* 32(2):219-229; 1975.

The uptake of 3-methylcholanthrene (MCA) and its metabolism to water-soluble derivatives were both determined in organ cultures of C3H and R strain of mouse and Lister rat tissues, including prostate, skin, lung and skeletal muscle. All tissues concentrated the carcinogen from the medium and metabolized part of it to water-soluble compounds. The influence of serum on MCA uptake was examined by incubating explants of rat and mouse prostates for 20 hr with 2.0 $\mu\text{g/ml}$ ^3H -MCA at serum concentrations varying from 0%-20%. The uptake of ^3H -MCA was highest in the absence of serum and declined with rising serum concentration. Except for skeletal muscle, ^3H -MCA uptake was consistently higher in the murine tissues. The uptake of the hydrocarbon by rat and mouse prostates rose rapidly with time, reaching a maximum after 18 hr incubation; the amounts of carcinogen in the tissue then declined and remained at a lower level for the rest of the observation period. The major part of the radioactivity was released within five hours of transferring the explants to medium without the tracer; 25-40% of the peak concentration of carcinogen, however, still remained in the tissue and further medium changes could not remove any more. Addition of unlabeled MCA to the initial incubation increased the radioactivity taken up and caused substantially larger quantities of the carcinogen to be retained after the medium had been changed. The explants converted between 15% and 30% of the MCA, which they had incorporated to water-soluble derivatives within 48 hr, but there was no obvious rela-

relationship between the amounts of hydrocarbon taken up by the different tissues and the proportions metabolized. Seventy percent of the MCA in the explants remained unconverted 28 hr after its removal from the medium, suggesting that intact tissues are able to concentrate and retain MCA for a considerable time without metabolizing all of it.

- 6092 EFFECT OF 3-METHYLCHOLANTHRENE PRETREATMENT ON GLUCURONIDATION AND SULFATION IN PERFUSED RAT LIVER. (Eng.) Hamada, N. (Grace Cancer Drug Center, Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14203); Gessner*, T. *Drug Metab. Dispos.* 3(5):407-416; 1975.

The metabolism of *p*-nitro[¹⁴C]phenol (PNP) was studied in the perfused liver of male Sprague-Dawley rats. Metabolites were identified in perfusate and bile. The perfusion system containing 0.5 mM PNP, at the start, converted the phenol within two hours to *p*-nitrophenyl glucuronide (PNPGA), 31.4% in perfusate and 21% in bile; *p*-nitrophenyl sulfate (PNPS), 22% in perfusate; and *p*-nitrophenyl glucoside (PNPG), between 2 and 4% in perfusate. Biliary excretion of PNPS and PNPG accounted for less than 2% of PNP. An apparent maximal rate of PNPGA synthesis by the perfused liver, estimated from the rates of appearance of PNPGA in perfusate and bile, corresponded well to the glucuronyl transferase activities determined in "native" liver homogenates. Sulfation of PNP in the perfused liver exhibited two apparent maximal rates of synthesis, as determined from the rates of appearance of the metabolite in the perfusate. A slower rate (R_1) occurred when PNP concentration was between 0.13 and 0.5 mM, and a faster rate (R_2) when PNP was approximately between 0.025 and 0.13 mM in the perfusate. Possible significance of these findings is discussed. Pretreatment of rats with 3-methylcholanthrene (3MC), 50 mg/kg increased the apparent maximal rate of PNPGA production by the perfused liver by a factor of 1.7, and biliary excretion of PNPGA by a factor of 1.5. The latter increase is attributed to the increased rate of synthesis of the glucuronide rather than to an increase in the biliary transport maximum, because the 3MC treatment produced no significant effect on the biliary excretion of pre-formed PNPGA added to the perfusate. The 3MC-pretreatment increased the rate of sulfation of PNP by 1.5-fold, as judged by the increase in R_2 . This is apparently the first report of an increase in sulfation due to polycyclic hydrocarbon-pretreatment.

- 6093 FACTORS AFFECTING METABOLISM AND MUTAGENICITY OF DIMETHYLNITROSAMINE AND DIETHYLNITROSAMINE. (Eng.) Frantz, C. N. (Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, N.C. 27709); Mallin*, H. V. *Cancer Res.* 35(9):2307-2314; 1975.

An attempt to relate a specific mammalian enzyme activity to dimethylnitrosamine (DMN) mutagenicity is reported. Microsomes were prepared from livers of CD-1 male rats and several strains of mice. Sterile techniques were used. *Salmonella typhimurium* G46 reversions to histidine independence were used as measures of mutagenicity. Mutagenesis from

microsomal metabolism of DMN was completely inhibited by 1 mM 2-diethylaminoethyl-2,2-diphenylvalerate, indicating that the reaction leading to mutagenicity involves hydroxylation. DMN demethylase activity correlated well with mutagenic activity in parallel assays with the same microsomes. Most of the enzymatic activity was found in the microsomal fraction. Induction with both phenobarbital and 3-methylcholanthrene (3-MC) increased rat and mouse liver DMN demethylase activity. Mouse liver microsomes from the C57BL/6 strain demethylated DMN at a markedly lower rate than microsomes from the C3H strain, but after 3-MC induction the relationship was reversed. Strain differences in activation of DMN were not found in the activation of diethylnitrosamine to a mutagen. Hepatic dealkylation of DMN and diethylnitrosamine to active mutagenic metabolites was increased in both rats and mice by both 3-MC and phenobarbital induction. The correlation of mutagenicity with DMN demethylase activity (formaldehyde production) indicates that demethylation is rate-limiting for DMN mutagenesis in this system.

- 6094 LONG-TERM TOXICITY STUDIES ON OXIDATION HAIR DYES. (Eng.) Burnett, C. (Cosmet. Toiletry Fragrance Assoc., Washington, D. C.); Larman, B.; Giovacchini, R.; Wolcott, G.; Scala, R.; Keplinger, M. *Food Cosmet. Toxicol.* 13(3): 353-357; 1975.

The effect of oxidation hair dyes applied in a manner approaching that of actual use by humans was studied in mice. Three oxidation hair dye formulations, mixed with hydrogen peroxide as in use, were tested for long-term toxicity and carcinogenic activity by topical application to groups of 100 (Swiss Webster) mice weekly or every alternate wk for 18 mo. Chemical intermediates present in the formulations were *p*-phenylenediamine, 2,5-toluenediamine sulfate, resorcinol, *m*-phenylenediamine, 2,4-diaminoanisole sulfate and 2,4-toluenediamine. Moderate alopecia occurred during the first five months in about 50% of mice treated weekly; after 11 mo hair growth appeared normal. Microscopic examination of skin sections at autopsy showed normal skin in all mice in these groups. In this study none of the formulations produced evidence of systemic toxicity or carcinogenicity.

- 6095 CARCINOGENICITY AND MUTAGENICITY TESTS OF SOME HAIR COLOURANTS AND CONSTITUENTS. (Eng.) Searle, C. E. (Med. Sch., Univ. Birmingham, England); Harnden, D. G.; Venitt, S.; Gyde, O. H. B. *Nature* 255(5508):506-507; 1975.

The long term carcinogenic and mutagenic effects of two 'semipermanent' hair colors are being investigated. These colors, as well as nine similar hair colors, were also subjected to mutagenicity testing in bacteria. Dye J contains nitrophenylenediamines and Dye K contains an azo-dye metal derivative and an aminonitrophenol. The dyes are being applied repeatedly (simulating normal human use) to skin of A and DBA mice. Malignant tumors in J-treated DBA mice have so far occurred in five out of 48 mice

and in two of 35 DBA mice treated with K dye. Four of 52 A strain mice developed tumors after treatment with J dye and three of 32 mice treated with K dye have developed tumors. The minimum exposure times varied considerably with strain and dye. In the DBA strain treated with J dye the range was 26-61 wk; with K dye the range was 41-47 wk. A strain mice treated with J dye took 48-59 wk to develop tumors, while those treated with K dye took 38-72 wk. Tumors were mostly malignant lymphomas involving the spleen and some liver infiltration. No skin lesions were found. The organisms used in mutagenicity tests were *Escherichia coli* WP2, WP2 *uvrA*, and WP2 *exrA*, and *Salmonella typhimurium* TA1535, TA1537, and TA1538. Negative results were obtained in those bacteria which reverted to base-pair substitution. Seven of 11 colors were strongly mutagenic in *S. typhimurium* TA1538, and of these, two were weakly mutagenic to TA1537 (one of these was dye J). The dyes 2-nitro-*p*-phenylenediamine (2-NPPD) and 4-nitro-*o*-phenylenediamine (4-NOPD) were mutagenic to both TA1538 and TA1537, with 4-NOPD three times more potent than 2-NPPD. Microsomal action was not required. All colors examined contained either or both 4-NOPD or 2-NPPD. No chromosome damage was noted at dosages used but mitotic delay and toxicity was apparent. The long-term use of these colorants may prove hazardous.

6096

PRELIMINARY STUDIES OF THE FATE OF INHALED VINYL CHLORIDE MONOMER IN RATS.

(Eng.) Hefner, R. E., Jr. (Health Environ. Res., Dow Chem. U.S.A., Midland, Mich.); Watanabe, P. G.; Gehring, P. J. *Ann. N.Y. Acad. Sci.* 246:135-148; 1975.

The fate of vinyl chloride monomer (VCM) in male Sprague-Dawley rats exposed *via* inhalation (50.5-15,000 ppm for 52.5 min to 5 days) was investigated, as were its effects on liver sulfhydryl levels. In some experiments, the rats were pretreated with pyrazole (320 mg/kg, ip 1 hr before exposure), ethanol (5 ml/kg, ip, 1.5 hr before exposure), or β -diethylaminoethyl-diphenylpropylacetate (SKF 525-A, 75 mg/kg, ip, 0.5 hr before exposure). Rats exposed to VCM in concentrations below 100 ppm metabolized the compound fairly readily in accordance with first-order kinetics, the half-life being 86 min. In animals exposed to concentrations exceeding 220 ppm, the half-life was increased to 261 min. Pyrazole inhibited the metabolism of 65 and 1,234 ppm VCM by 71.2 and 86.9%, respectively. Ethanol inhibited the metabolism of 56, 97, 1,025, and 1034 ppm by 96.0, 82.9, 46.5, and 35.7%, respectively. SKF 525-A did not inhibit the metabolism of 65 ppm VCM, but it did inhibit the metabolism of 1,038 ppm by 18.8%. Exposure to VCM reduced the nonprotein sulfhydryl concentration of the liver in a manner that was not definitely associated with dose. The reduction in concentration tended to become less pronounced with repeated daily exposures. Ethanol significantly reduced the VCM-induced depression in hepatic nonprotein sulfhydryl. Monochloroacetic acid was found in the urine of animals exposed to 5,000 ppm VCM daily for nine weeks; in rats exposed to 49 ppm VCM, the compound was metabolized to polar products that were excreted predominantly in the urine. These

products appeared to be derived after the initial metabolism of VCM and subsequent conjugation of the products with glutathione and/or cysteine through covalent binding with the sulfhydryl. A small but significant fraction of VCM was metabolized to CO₂ and expired, and an even smaller, but still significant, fraction was retained in the tissues, primarily the liver. It is suggested that in rats exposed to concentrations of VCM below 100 ppm, VCM is predominantly metabolized *via* sequential oxidation to 2-chloroethanol, chloroacetaldehyde, and monochloroacetic acid by the alcohol dehydrogenase pathway. Little or no monochloroacetic acid is formed at low doses. At 220 ppm, metabolism by the more rapid alcohol dehydrogenase pathway appears to be saturated, and metabolism *via* oxidation of the accumulating 2-chloroethanol may occur.

6097

DISCUSSION OF PRECEDING PAPER. (Eng.)

Oster, G. (Mt. Sinai Sch. Med., City Univ. New York, N.Y.). *Ann. N.Y. Acad. Sci.* 246:149; 1975.

The metabolism and polymerization of vinyl chloride and the possible health hazards posed by polyvinyl chloride are discussed. Vinyl chloride binds to serum albumin, which is synthesized at specific regions of the liver; vinyl chloride may thus be localized in these regions. It is likely that vinyl chloride is metabolized, at least in the initial stages, *via* the cytochrome P-450 system in the endoplasmic reticulum of the liver cells. Liver microsomes will initiate the polymerization of a vinyl monomer. Vinyl chloride could polymerize in the lipid portions of liver cell organelles only if the monomer concentration is high; otherwise, the monomer would undergo reactions such as dehalogenation and epoxide formation. During the polymerization of vinyl chloride, polyvinyl chloride precipitates and entrains monomer. Warming polyvinyl chloride pipe also releases some entrained monomer. During the polymerization reaction, there is also entrapment of free radicals, which have been demonstrated in polyvinyl dust. Workers in polymerization plants are exposed not only to high levels of monomer, but also to high concentrations of these free radical-laden dust particles. The possible harmful effects of this dust should be considered.

6098

CYTOLOGIC CHANGES INDUCED IN RAT LIVER CELLS BY SHORT-TERM EXPOSURE TO CHEMICAL SUBSTANCES. (Eng.)

Hitachi, M. (Cancer Inst., Tushima-ku, Tokyo 170, Japan); Yamada, K.; Takayama, S. *J. Natl. Cancer Inst.* 54(5):1245-1247; 1975.

Cytogenetic changes induced in the livers of male Donryu rats by three-week exposure to hepatocarcinogens and nonhepatocarcinogens administered in the diet or drinking water were investigated. The hepatocarcinogens included diethylnitrosamine, 3'-methyl-4-dimethylaminoazobenzene, 4-dimethylaminoazobenzene, 2,7-acetylaminofluorene, 2-acetylaminofluorene, and aflatoxin B₁. All the hepatocarcinogens markedly increased the mitotic rate in the liver. Except for α -benzene hexachloride and nitrosobutylurea, the six nonhepatocarcinogens tested did not appreciably increase the mitotic rate. Cy-

togenetic analyses on the ploidy rate and chromosome abnormalities evidenced qualitative differences among mitotic liver cells in animals treated with hepatocarcinogens and nonhepatocarcinogens. After treatment with hepatocarcinogens, almost all dividing liver cells were diploid and usually had chromosome abnormalities (trisomy or monosomy of chromosomes). The active cell proliferation and chromosome changes in liver cells observed after the administration of hepatocarcinogenic substances may have some relation to an essential process in hepatocarcinogenesis.

- 6099 TUMOR INDUCTION BY CARCINOGENIC AGENTS IN AQUARIUM FISH. (Eng.) Pliss, G. B. (Petrov Res. Inst. Oncol., Leningrad, USSR); Khudoley, V. *J. Natl. Cancer Inst.* 55(1):129-136; 1975.

The effects of nine carcinogens on 1,220 guppies [*Poecilia reticulata* (*Lebistes reticulatus*)] and 40 zebra fish (*Danio rerio*) were studied. Exposure techniques included skin application, im and ip injections, feeding, implantation in pellets, and dissolving of the compound in the aquarium water. 7-12-Dimethylbenz[a]anthracene, 3-methylcholanthrene, and benzidine produced no tumors in the fish. N-2-Fluorenylacetylamide, o-aminoazotoluene, 4-dimethylaminoazobenzene, diethylnitrosamine, and dimethylnitrosamine induced tumors in the livers of some of the fish. Of the multiple exposure techniques used, the most effective procedure was dissolving the carcinogen in the water. These neoplasms included cholangiomas, hepatoadenomas, cholangiocarcinomas, and hepatocellular cancers. Nitrosomorpholine caused not only hepatic tumors in guppies and zebra fish but also intestinal adenocarcinomas and poorly differentiated connective-tissue lesions in the abdominal cavities of zebra fish. Experimental induction of tumors in aquarium fish offers wide possibilities for comparative cancer research. Fish are a suitable model for the testing of compounds for carcinogenic activity and for the screening of environmental carcinogens.

- 6100 THE MEASUREMENT OF CHEMICALLY-INDUCED DNA REPAIR SYNTHESIS IN HUMAN CELLS BY BND-CELLULOSE CHROMATOGRAPHY. (Eng.) Scudiero, D. (Dept. Microbiology, Univ. Chicago, Chicago, Ill. 60637); Henderson, E.; Norin, A.; Strauss, B. *Mutat. Res.* 29(3):473-488; 1975.

A chemically simple method for the study of repair in cell cultures is described. Repair synthesis in human cells in tissue culture can be readily separated from semi-conservative DNA synthesis with the aid of a benzoylelated naphthoylated DEAE cellulose (BND-cellulose) column. The cells are incubated with a radioactive DNA precursor during treatment with a repair-inducing agent. An inhibitor of semi-conservative DNA synthesis (hydroxyurea) is added to slow the progression of the DNA growing point. The cells are then lysed with ribonuclease and pronase, after which the lysates are sheared and passed through the BND-cellulose column. Nonreplicating bulk DNA will wash through the column with NaCl, and repair can be measured directly from the NaCl eluate of the column. DNA fragments containing single-stranded regions adhere to the column and can

be eluted with 50% formamide; this formamide eluate can then be used to measure repair in the growing point region. This method was applied to the study of RAJ1, XP₃ BE-L₃ (xeroderma pigmentosum lymphoblast line), and HEp2 cells treated with methyl methane-sulfate (MMS), methylnitrosourea (MNNU), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), 7-bromomethyl benz-(α)anthracene (BMBA), and N-acetylaminofluorene (AAAF) in the presence of hydroxyurea and deoxyguanosine and deoxythymidine labels. The results indicate the ability of the method to distinguish between repair and semi-conservative synthesis and to measure repair in the growing point region. The method is adaptable to a large number of samples and can be used with isotopes other than deoxythymidine so that measurements of excision repair need not be dependent on the presence of an active thymidine kinase in the cells being treated.

- 6101 THE CRYSTAL STRUCTURE OF A URACIL-ACETONE PHOTOADDITION PRODUCT. (Eng.)

Stein, M. T. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, Mass. 02139); Berman, H. M.; Varghese, A. J. *Biochim. Biophys. Acta* 407(4): 377-383; 1975.

Crystallographic study of the photoaddition product of uracil (or cytosine) and acetone was undertaken to confirm its structure and to determine the detailed stereochemistry of the two rings. Light amber crystals of the photoaddition product were grown which were triclinic, in the space group P1, Z=2, and with cell dimensions $a = 5.908(4)$, $b = 12.102(5)$, $c = 6.253(3)$ Å, $\alpha = 94.08(4)$, $\beta = 113.45(4)$, $\gamma = 96.84(4)$, and $V = 403.8(4)$ Å³. The structure was solved by direct methods and refined by a full-matrix least-squares procedure to the final residual $R = 0.069$. Eight of the ten hydrogen atoms were located from a difference map, and were refined isotropically. Both the uracil ring and the oxetane ring were found to be nearly planar, the angle between these planes being 121°. The structure was aligned so that there were stacked layers of pyrimidine rings, rows of oxetanes, and a strongly hydrophobic region of methyl groups. Although this uracil photoaddition product contained two asymmetric carbon atoms, C(5) and C(6), only the *cis-syn* isomer was formed, and in the centro-symmetric crystal both enantiomers were present. These isomers were designated 5(S),6(R) and 5(R),6(S). The 5(R),6(S) form had the oxetane ring above and to the right of the plane of the uracil ring when the N(1) atom was at the bottom. The 5(R),6(S) form would have the oxetane ring below the uracil ring and the N(1) atom again at the bottom. The replacement of thymine by the 5(S),6(R) form would be sterically incompatible with the ribose phosphate backbone of either A-DNA or B-DNA. The other form, 5(R),6(S), however, could replace thymine in the double helix without substantial conformational change. Both pyrimidine-purine and pyrimidine-pyrimidine sequences could accommodate this change, but the methyl groups and the oxetane ring would be likely to interfere with the binding of protein to the major groove in both A-DNA and B-DNA and in RNA. It is suggested, therefore, that this optical isomer may serve as a

useful structural probe for the binding of proteins to the major groove of the double helix if it can be incorporated into DNA.

- 6102 LONG-TERM TOXICITY OF INDIGO CARMINE IN MICE. (Eng.) Hooson, J. (British Ind. Biol. Res. Assoc., Carshalton, England); Gaunt, I. F.; Kiss, I. S.; Grasso, P.; Butterworth, K. R. *Food Cosmet. Toxicol.* 13(2):167-176; 1975.

Because no previous data existed on the effects of long-term feeding of indigo carmine in mice, groups of 30 male and 30 female Charles River CD1 mice were fed diets containing 0.2, 0.4, 0.8, or 1.6% indigo carmine for 84 wk. Sixty male and 60 female mice served as controls. During weeks 26 and 52 of treatment, blood samples were obtained from ten mice of each sex from the control group and from the groups being fed 0.8% and 1.6% indigo carmine. Hemoglobin concentration, packed cell volume, total RBC and total WBC were determined from these samples. Hemoglobin was also determined in surviving animals after 84 wk. At this time the animals were killed and autopsied; the heart, liver, spleen and kidneys were then weighed. Samples of these organs together with brain, stomach, intestine, pituitary, salivary glands, thyroid, thymus, adrenals, lymph nodes, pancreas, spinal cord, ovaries, uterus, testes, bladder, skeletal muscle and any organs with abnormal appearance were examined histopathologically. The treatment had no effects on the weights or on the incidence of tumors in these organs. There was also no effect on the death rate or on body weight gain in the animals. A slight anemia occurred in mice given diets containing 0.8% or 1.6% indigo carmine. Since this occurred only at wk 26, and not at wk 52, the authors conclude that the anemia was a chance-occurrence. It is concluded that long-term feeding of indigo carmine to mice at dietary levels of up to 1.6% did not exert any carcinogenic effect. The "no-untoward-effect" level in this study was 0.4% of the diet.

- 6103 CARCINOGENESIS AND CELLULAR INJURY: THE EFFECT OF ETHIONINE ON RIBONUCLEIC ACID SYNTHESIS IN RAT LIVER. (Eng.) Swann, P. F. (Middlesex Hosp. Medical Sch., London W1P 5PR, U.K.); Peacock, A. C.; Bunting, S. *Biochem. J.* 150(3):335-344; 1975.

The effect of ethionine on RNA synthesis in rat liver was studied in female Sprague-Dawley rats injected ip with 750 mg/kg DL-ethionine before iv injections of [6-¹⁴C]orotic acid (100 μ Ci) or [5-³H]orotic acid (200 μ Ci). The rats were killed 30, 90, or 180 min after receiving [5-³H]orotic acid and three hours after receiving [6-¹⁴C]orotic acid. By one hour after ethionine administration, the appearance of newly synthesized 18S and 28S ribosomal RNA (rRNA) was completely inhibited. This was not caused by inhibition of RNA synthesis because synthesis of the large ribosomal precursor RNA (45S) and of transfer RNA continued. Cleavage of 45S RNA to 32S RNA also occurred, but there was no evidence for the accumulation of mature or immature rRNA in the nucleus. The effect of ethionine on the maturation of rRNA was not mimicked by an inhibitor of protein synthesis (cycloheximide, 1.5 mg/kg) or an inhibitor of poly-

amine synthesis [methylglyoxal bis(guanyldihydrazone), 80 mg/kg]. Unlike the ethionine-induced inhibition of protein synthesis, this effect was not prevented by the concurrent administration of inosine (570 mg/kg). A similar effect could be induced in HeLa cells by incubation for one hour in medium lacking methionine. The ATP concentration in these cells was normal. On the basis of these two observations, it is concluded that the effect of ethionine on rRNA maturation is not caused by an ethionine-induced lack of ATP. It is suggested that ethionine, by lowering the hepatic concentration of S-adenosylmethionine, prevents methylation of the ribosomal precursor. The methylation is essential for the correct maturation of the molecule; without methylation complete degradation occurs.

- 6104 THE EFFECT OF CUPRIC ACETATE ON ETHIONINE METABOLISM. (Eng.) Brada, Z. (Papanicolaou Cancer Res. Inst. Miami, Miami, Fla. 33136); Altman, N. H.; Bulba, S. *Cancer Res.* 35(11/Part 1):3172-3180; 1975.

The effects of cupric acetate, a potent inhibitor of ethionine carcinogenesis, on ethionine metabolism was studied in female CFN rats which were divided into four groups as follows: (a) fed a semisynthetic diet, C-24, only; (b) fed C-24 plus 0.30% DL-ethionine; (c) fed C-24, 0.30% DL-ethionine, and 0.30% cupric acetate; and (d) fed C-24 and 0.30% cupric acetate. In acute experiments, L-ethionine was given by gavage (12.5 mg/100 g) alone or together with cupric acetate solution (12.5 mg/100 g). The concentration of S-adenosylethionine in the liver was substantially increased by combined ethionine and cupric acetate feeding over that obtained with ethionine feeding alone. The highest S-adenosylethionine concentration in liver was observed five hours after po administration of ethionine-cupric acetate. The absorption of L-[ethyl-1-¹⁴C]ethionine from its copper complex was studied by a direct measurement of the remaining radioactive ethionine in the gastrointestinal contents. The results indicate that the absorption of ethionine from ethionine-cupric acetate was significantly decreased in the first hour after administration. A significant portion of ethionine administered in its free form was not absorbed and was later excreted in the feces. With free ethionine, absorption was completed after two hours, but the absorption process took almost 24 hr when ethionine-cupric acetate was given. There was decreased absorption of ethionine from ethionine-cupric acetate in animals with higher body weight. When ethionine was administered alone, it was metabolized in the intestinal lumen as demonstrated by the analysis of the soluble intestinal contents; the presence of cupric acetate inhibited this process. The chromatographic analysis of ethionine metabolites in the urine of rats treated with ethionine-cupric acetate revealed an increased excretion of ethionine sulfoxide and other ethionine metabolites at the expense of N-acetylethionine sulfoxide. The increased concentration of S-adenosylethionine in the liver in chronic experiments may be, at least partly, a result of a diminished capacity of the rat to detoxify ethionine sulfoxide, which is considered the main reserve

pool of ethionine for the maintenance of a high level of *S*-adenosylethionine. It is suggested that the protective effect of cupric acetate on tumor formation may be explained in general pathological terms by the increased toxicity of ethionine-cupric acetate, which could change the reactivity of liver tissue to such an extent that it would result in a modification of the quality of the toxic effect.

- 6105 HEPATOMA ASSOCIATED WITH ANDROGENIC STEROIDS. (Eng.) Johnson, F. L. (Univ. Washington Sch. Medicine, Seattle, Wash. 98122); Bruguera, M. *Lancet* 1(7919):1294-1295; 1975.

The author of a letter to the editor takes exception to the conclusion drawn in a previous review on liver tumors seen in patients receiving androgenic steroids; in this review it was stated that there were only "two acceptable cases of hepatocellular carcinoma in association with antigenic steroid treatment". Other pathologists who have reviewed the original histopathological sections discussed in the review have found that the tumors were histologically indistinguishable from true hepatocellular carcinoma. The practical implication of hepatic tumors found in patients on these drugs should not be ignored. Regression has been described in three patients when the androgenic-anabolic steroids were stopped. The initial management of such a patient who develops a space-occupying hepatic lesion with the histological characteristics of hepatocellular carcinoma is stopping the agent for a period of observation. Such a period of observation may prove fatal, however, in the woman on oral contraceptives who has a space-occupying liver lesion. Four of 13 such patients have died of intractable bleeding. Immediate operation is suggested as the treatment of choice in this case. It is concluded that until androgenic steroid-induced tumors are proved to be nonmalignant, athletes taking the steroids should be made aware of the possible serious side effects.

- 6106 INFLUENCE OF SEX AND SEX HORMONES ON TRANSPLANTABLE HEPATOCELLULAR CARCINOMA IN THE RAT. (Eng.) Reuber, M. D. (11014 Swansfield Road, Columbia, Md. 21044). *Pathol. Microbiol. (Basel)*. 42(1):59-65; 1975.

Male and female F₁ hybrids from male AXC and female Sprague-Dawley rats were inoculated sc with tissue from hepatocellular carcinoma-35 and studied for the time of appearance of tumors and the number of successful tumor takes. Palpable growth of tumor transplants appeared two weeks earlier in male animals, but the number of successful growths was no greater than in females. The animals were then divided into the following groups of 6-10 rats: intact and castrated males and females, castrated females given testosterone (20 mg/100 g,sc), and castrated males given diethylstilbestrol (15 mg/100 g,sc). Gonadectomy was performed when the tumor transplants reached 1.0-1.5 cm in size. There was little difference in tumor growth rate in intact or castrated male or female animals. The carcinoma in castrated female rats given testosterone was less differentiated histologically

than that in other groups, had more bile pigment, grew much more rapidly, metastasized sooner, and killed the host quickly. Bile was present in lung metastases. Exogenous diethylstilbestrol slowed the growth of the transplants and caused weight loss in castrated males. The weight loss was apparently related to the extensive necrosis of the carcinoma. These results indicate that previous studies concerned with the morphologic and biologic correlation of hepatic carcinogenesis in the rat would not have varied significantly if more males had been used as recipients of transplants.

- 6107 EXPERIENCE IN INDUSTRIAL EXPOSURE CONTROL. (Eng.) Rowe, V. K. (Dow Chem. U.S.A., Health Environ. Res., Midland, Mich.). *Ann. N.Y. Acad. Sci.* 246:306-310; 1975.

Industrial hygiene methods employed by the Dow Chemical Company provide a model upon which future environmental control systems can be based. The results of toxicological studies of vinyl chloride and vinylidene chloride since 1959 indicated an increased need for monitoring of these substances in the air. Dow widely uses combustion-conductivity analysis but gas chromatography and infrared spectrophotometry have also been recently employed. Time-weighted averages of vinyl chloride exposure that an employee would have in a given job can be computed. In 1959, it was established that this average exposure should not exceed 50 ppm vinyl chloride or 25 ppm vinylidene chloride for an eight-hour-day week. Exposure was 1-10.4 ppm for most employees in three monomer plants, but laboratory personnel were exposed to 30 ppm. While levels were only 1-5 ppm for most employees in the polymer plant, some areas showed as high as 150 ppm. Safe levels of any hazardous material must be established and maintained through appropriate engineering and monitoring. Corrective measures should be taken when breakdowns occur and a medical surveillance program must be supported. Vinyl chloride is processed in closed vessels with maximum ventilation, and process automation and remote operation are emphasized. The number of samples for control analysis is minimized, manual collection is reduced by using on-line gas chromatography, and a closed-loop sampling system is used. Polymerization vessels must contain vinyl chloride concentrations of less than 50 ppm before entry for cleaning and air purge must be maintained during the operation.

- 6108 EXPERIENCES WITH THE DOMINANT LETHAL TEST IN FEMALE MICE: EFFECTS OF ALKYLATING AGENTS AND ARTIFICIAL SWEETENERS ON PRE-OVULATORY OOCYTE STAGES. (Eng.) Machemer, L. (Bayer AG, Institut für Toxikologie, Wuppertal-Elberfeld, W. Germany); Lorke, D. *Mutat. Res.* 29(2):209-214; 1975.

A study of dominant lethal effects in female mice was undertaken in an attempt to develop a procedure for screening potential mutagenic substances early in the product development stages. Female mice were considered to be especially useful for these purposes because (a) the preovulatory oocytes are especially sensitive to mutagenic influences, and

(b) the post-dictyotene oocytes, not being subject to selection and elimination before fertilization, may reveal mutagenic effects directly and unrestrictedly. In the procedure developed for screening purposes, vaginal smears were taken at about 3 p.m., and the estrus phases of the female mice were examined. Animals in pre-estrus received a single dose of the test compound, and at about 4 p.m. were mated with untreated males. Females that had a vaginal plug the following morning were rated as inseminated and remained in the trial. Two weeks after the appearance of the vaginal plug the females were sacrificed and dissected and evaluated as in the usual dominant lethal test. The screening procedure was tested with artificial sweeteners and alkylating agents. The following treatments induced dominant lethal effects: methyl methanesulfonate, 100 mg/kg im; cyclophosphamide, 200 mg/kg po and triaziquone, 0.25 mg/kg ip. The following agents were ineffective and may be classified as not mutagenic in this method: sodium cyclamate 10,000 mg/kg po; saccharine sodium, 10,000 mg/kg po; cyclohexamine sulfate 150 mg/kg po; and ethanol 5 ml/kg po. Several advantages are claimed for the proposed screening system; this includes the fact that if no lethal effect occurs, the absence of mutagenic action, and the absence of action on ovulation, fertilization, and cleavage can be deduced. If lethal effects are found, however, they do not prove mutagenic action; action on other processes of reproduction is also possible, and further studies using other test systems are necessary.

- 6109 BLADDER CANCER MORTALITY IN DIABETICS IN RELATION TO SACCHARIN CONSUMPTION AND SMOKING HABITS. (Eng.) Armstrong, B. (Radcliffe Infirmary, Oxford, England); Doll, R. *Br. J. Prev. Soc. Med.* 29(2):73-81; 1975.

The occurrence of bladder cancer was studied retrospectively in patients with diabetes mellitus in relation to saccharin consumption and smoking habits. The frequency with which diabetes mellitus was mentioned on the death certificates of 18,733 patients dying from bladder cancer in England and Wales from 1966-1972 (inclusive) was compared with that of 19,709 patients dying from other cancers (excluding cancer of the lung and pancreas). Data on saccharin consumption were obtained from questionnaires mailed to a random sample of 200 diabetics and to 200 age- and sex-matched control patients. Data on the smoking habits of diabetics were obtained from the Boston Collaborative Drug Surveillance Program. The estimated relative risk of bladder cancer in diabetics was 0.98 with 95% confidence limits 0.70-1.38. There was no increase in risk of bladder cancer in patients with diabetes of long duration. Questionnaire returns indicated that diabetics consume substantially more saccharin than nondiabetics (diabetic men consumed 0-8.42 mg/kg daily, diabetic women 0-8.04 mg/kg; nondiabetic men consumed 0-1.58 mg/kg daily, nondiabetic women 0-6.47 mg/kg) and that the duration of regular saccharin use by diabetics was highly correlated with the duration of the diabetes. This study did not show evidence that consumption of above-average amounts of saccharin leads to bladder cancer in diabetics. The proportion of current smokers among diabetics was sig-

nificantly less than among nondiabetics. It is suggested that this may account for the low relative risk of lung cancer in diabetics.

- 6110 EVALUATION OF A NEW MODEL TO DETECT BLADDER CARCINOGENS OR CO-CARCINOGENS; RESULTS OBTAINED WITH SACCHARIN, CYCLAMATE AND CYCLOPHOSPHAMIDE. (Eng.) Hicks, R. M. (Middlesex Hosp. Medical Sch., London, W1P 7LD, Great Britain); Wakefield, J. St. J.; Chowaniec, J. *Chem. Biol. Interact.* 11(3): 225-233; 1975.

A sensitive model was designed to detect potential weak bladder carcinogens or cocarcinogens. The test compound is given to Wistar rats which have received a single intravesicular initiating but noncarcinogenic, dose of *N*-methyl-*N*-nitrosourea (MNU, 2.0 mg). The model was used to investigate two compounds currently under suspicion as weak bladder carcinogens, sodium saccharin and sodium cyclamate; and one compound known to be cytotoxic but not carcinogenic for the bladder epithelium, cyclophosphamide. The three compounds were also tested as solitary carcinogens in animals not pretreated with MNU. At very high dose levels, sodium saccharin (2.0 or 4.0 g/kg/day for life) and sodium cyclamate (1.0 or 2.0 g/kg/day for life) were weak solitary carcinogens producing four bladder tumors in 253 mice and three in 228, respectively. The first of these tumors did not appear for more than 80 wk. When tested in the MNU rat model, more than half the animals receiving either sodium saccharin or sodium cyclamate developed bladder tumors from ten weeks onward. By contrast, cyclophosphamide failed to produce any tumors when tested, either as a solitary carcinogen (18 monthly ip injections of 100 mg/kg) or in the MNU rat model (single ip injection of 200 mg/kg, given either two weeks before or two weeks after intravesicular dose of 2.0 mg MNU). The doses of saccharin and cyclamate used were far higher than those consumed by man, including diabetics, and these results should not be directly extrapolated to man without careful consideration of many other factors including negative epidemiological findings. The theoretical basis of the model is discussed, and also the relevance, in terms of environmental human exposure, of detecting compounds having a synergistic effect with other known bladder carcinogens. It appears that this model can be used to detect a carcinogenic or cocarcinogenic potential in compounds that are organotropic for the bladder more rapidly and with fewer animals than if the compounds are tested as solitary carcinogens by more conventional methods.

- 6111 A CARCINOGENICITY STUDY OF COMMERCIAL SACCHARIN IN THE RAT. (Eng.) Munro, I. C. (Bureau Chemical Safety, Health Protection Branch, Ottawa, Canada); Moodie, C. A.; Krewski, D.; Grice, H. C. *Toxicol. Appl. Pharmacol.* 32(3):513-526; 1975.

The carcinogenicity of commercial saccharin was investigated in rats. Groups of 60 male and 60 female Charles River rats were fed diets containing sodium saccharin to provide daily doses of 0, 90, 270, 810, or 2,430 mg saccharin/kg/day. The ani-

mals were treated for a period of 26 mo. Food consumption, body weight, and clinical examinations were conducted weekly on all rats. The animals were free of the bladder parasite *Trichisomoides crassicauda*. Four bladder tumors were found in treated animals: one male and one female from the 90-mg/kg group and two males given 810 mg/kg. The tumors were transitional cell papilloma, none of which were invasive. Three bladder calculi were observed grossly and several others were noted in urine samples examined microscopically. The presence of bladder calculi was associated with neither saccharin treatment nor with the presence of bladder tumors. Saccharin administration thus does not appear to be accompanied by an increase in tumor incidence, although high doses were associated with reduced body weight in both sexes and decreased longevity in male rats.

- 6112 DIRECT TRIMETHYLSILYLATION OF PHENANTHRENE AND ITS PRODUCTS--AN ABNORMAL SILYLATION OF PHENANTHRENE.. (Eng.) Yang, M.-H. (Dept. Chemistry, Natl. Taiwan Univ., Taipei, Nationalist Republic of China); Liu, S.-L. *J. Chin. Chem. Soc. (Taipei)* 22(1):41-47; 1975.

Direct trimethylsilylation of phenanthrene was undertaken using different molar ratios of phenanthrene/metallic sodium/trimethylchlorosilane. Small metallic sodium pieces were added to 15 g dry phenanthrene in 80 ml anhydrous THF. Trimethylchlorosilane in anhydrous THF was slowly added. The reaction mixture was hydrolyzed with 3% aqueous HCl solution. After extraction by THF and evaporation of solvent, a crude product of greenish-yellow oil with greenish-blue fluorescence was obtained, the composition of which was estimated by gas chromatography. Other than a variation in their relative amounts, the reaction products were not affected by variation in the reactant molar ratios. The most reproducible results were obtained when the molar ratio of phenanthrene/metallic sodium/trimethylchlorosilane was 1:3:3. The main reaction product was characterized as 9,9-bis(trimethylsilyl)-10,10-dihydrophenanthrene or 9,10-bis(trimethylsilyl)-9,10-dihydrophenanthrene by NMR spectroscopy. Three minor components were characterized by silicon analysis, gas chromatography-mass spectra, and NMR spectra and assumed to be: 9-trimethylsilyl-9,10-dihydrophenanthrene, 9,9,10-tris(trimethylsilyl)-10-hydrophenanthrene, and x,9,10-tris(trimethylsilyl)-9,10-dihydrophenanthrene. These silylated products changed into a red oil during longterm storage in the atmosphere under light exposure apparently as a result of desilylation and auto-oxidation.

- 6113 SURFACE PROPERTIES OF PHORBOL ESTERS AND THEIR INTERACTION WITH LIPID MONOLAYERS AND BILAYERS. (Eng.) Jacobson, K. (Rosewell Park Memorial Inst., Buffalo, N.Y. 14263); Wenner, C. E.; Kemp, G.; Papahadjopoulos, D. *Cancer Res.* 35(11/Part 1):2991-2995; 1975.

The surface properties of 12-O-tetradecanoyl-phorbol-13-acetate (a potent tumor-promoting agent), phorbol-12,13-didecanoate (active stereoisomer), and 4- α -phorbol-12,13-didecanoate (inactive stereoisomer)

were studied, and their interaction with phospholipid monolayers and bilayers were characterized. For a demonstration of phorbol-12,13-didecanoate binding to phospholipid bilayers, sonically treated and centrifuged vesicles, composed of egg phosphatidylcholine and beef brain phosphatidylserine (9/1 molar ratio, 7.15 μ M/ml, total phospholipid) were incubated with 5.6×10^{-7} M [3 H]phorbol-12,13-didecanoate for 12 hr at 4 C. The suspension was eluted over a Sephadex G-50 column. 12-O-Tetradecanoyl-phorbol-13-acetate was surface active and occupied a limiting area of 62 \AA^2 /molecule in monolayers at the air-water interface. The interfacial tension of aqueous 12-O-tetradecanoyl-phorbol-13-acetate solutions was decreased by increasing the bulk-phase 12-O-tetradecanoyl-phorbol-13-acetate concentrations up to 2×10^{-6} M, beyond which no further decreases were observed. The apparent aqueous solubility limit of the more hydrophobic phorbol-didecanoate is 5×10^{-8} M. Interaction of 12-O-tetradecanoyl-phorbol-13-acetate with egg phosphatidylcholine monolayers at the air-water interface was shown by an increase in the surface pressure of the monolayer from 22 dynes/cm, initial film pressure, to 34 dynes/cm 90 min after introducing 12-O-tetradecanoyl-phorbol-13-acetate into the aqueous subphase. The binding of [3 H]-phorbol-12,13-didecanoate to phospholipid vesicles was shown by gel filtration chromatography. Differential scanning calorimetry also indicated that the addition of either 12-O-tetradecanoyl-phorbol-13-acetate or 4- α -phorbol-didecanoate to phospholipid bilayers resulted in a marked reduction of the enthalpy of the minor transition of dipalmitoylphosphatidylcholine liposomes. Several fluorescence polarization probes indicated that 12-O-tetradecanoyl-phorbol-13-acetate does not affect membrane fluidity. The presence of 12-O-tetradecanoyl-phorbol-13-acetate induced no measurable change in the cation permeability of phospholipid vesicles, the conductance of planar bilayer membranes, or the electroporetic mobility of negatively charged liposomes. The lack of a specific effect with bilayers alone, combined with the documented physiological effects at low 12-O-tetradecanoyl-phorbol-13-acetate concentrations, suggests the possibility of a specific membrane component as the receptor for this compound in the plasma membrane.

- 6114 THE EFFECTS OF SEVERAL CROTON OIL CONSTITUENTS ON TWO TYPES OF DNA REPAIR AND CYCLIC NUCLEOTIDE LEVELS IN MAMMALIAN CELLS *IN VITRO*. (Eng.) Trosko, J. E. (Dept. Human Development, Michigan State Univ., E. Lansing, Mich. 48823); Yager, J. D., Jr.; Bowden, G. T.; Butcher, F. R. *Chem. Biol. Interact.* 11(3):191-205; 1975.

The effects of two potent tumor-promoting agents on two DNA repair mechanisms and cyclic nucleotide levels in mammalian cells were investigated. Human amnion (AV₃) cells were treated with low dose levels of either UV (254 nm, 10 erg/mm²/sec) or N-acetoxy-acetylaminofluorene. Subsequently, DNA excision repair as measured by unscheduled DNA synthesis was followed in the absence or presence of nontoxic levels of either 12-O-tetradecanoyl-phorbol-13-acetate (TPA, 0.001-1 μ g/ml), phorbol-12,13-dibenzoate (PDB, 0.0092-0.92 μ g/ml), both

potent tumor promoters, or phorbol (0.0059-0.59 µg/ml), a nonpromoter. Neither of these compounds inhibited DNA repair synthesis occurring in response to low doses of the carcinogenic agents. In addition, TPA did not inhibit "postreplication repair" in response to UV irradiation of growing Chinese hamster (V79-4) cells. However, both TPA and PDB did cause rapid dramatic increases in cyclic guanosine monophosphate levels in human amnion cells; phorbol had no effect. Neither of these compounds affected cyclic AMP. These results are discussed in light of a possible mechanism of the action of tumor promoters involving "postreplication repair".

- 6115 HISTOGENESIS AND GROWING PATTERNS OF LUNG TUMORS INDUCED BY POTASSIUM 1-METHYL-1,4-DIHYDRO-7-[2-(5-NITROFURYL)VINYL]-4-OXO-1,8-NAPHTHYRIDINE-3-CARBOXYLATE IN ICR MICE. (Eng.) Matsuzaki, O. (Sch. Medicine, Chiba Univ., Inohana 1-8-1, Chiba 280, Japan). *Cann* 66(3):259-267; 1975.

The effect of potassium 1-methyl-1,4-dihydro-7-[2-(5-nitrofuryl)vinyl]-4-oxo-1,8-naphththyridine-3-carboxylate (NFN) on ICR/JCL mice (45 males, 45 females) was investigated. A 0.01% solution of NFN administered po resulted in the development of tumors in the lung, forestomach, thymus, and other areas. Special attention was directed to the incidence and growing processes of the pulmonary tumors, which usually exhibited multicentric occurrence. Adenomatous hyperplasia and adenoma were observed in 22.2% of group A (surviving beyond the 15th wk, but dying by the 30th wk), 81.3% of group B (30-38 wk), and 91.2% of group C (38-54 wk). One case of carcinoma in group B and five cases in group C were also found. Most of adenomatous hyperplasia and adenomas developed approximately 30 wk after the beginning of administration, whereas the carcinomas developed after 36 wk. The incidence of tumors was much earlier in females than in males. The tumors originated from type B alveolar epithelial cells. The growth of type B alveolar epithelial cells was first noted as an adenomatous hyperplasia along the original alveolar walls, disintegrating and virtually replacing type A alveolar epithelial cells. Accordingly, adenoma noduli was formed by these proliferated type B alveolar epithelial cells. Atypical, basophilic cell clusters were present within the adenomas. It is suggested that carcinomas might have originated from these atypical type B alveolar epithelial cells.

- 6116 EFFECTS OF GALLIC ACID ON NITROSAMINE FORMATION. (Eng.) Walker, E. A. (International Agency for Res. on Cancer, 150 Cours Albert-Thomas, 69008 Lyon, France); Pignatelli, B.; Castegnaro, M. *Nature* 258(5531):176; 1975.

The effect of gallic acid on nitrosation of diethylamine was investigated with respect to the possibility that the formation of carcinogenic nitrosamines occurs *in vivo*. Nitrite (0.075 M) and diethylamine (0.5 M) in buffered solutions, were reacted with various concentrations of gallic acid (0, 0.0625, 0.0375, 0.025 and 0.0125 M). The reaction time was 30 min, after which the solution was made al-

kaline and extracted with methylene chloride. Nitrosamines concentration was determined using UV spectrophotometry and gas chromatography. Both nitrite and amine concentrations were determined to give a yield of nitrosodiethylamine. The results showed that gallic acid exerted a catalytic effect at pH 4. An increase in the formation of nitrosamine related linearly with a decrease of gallic acid. Caution is recommended towards the idea that formation of nitrosamines by natural phenols occurs *in vivo*. Nitrosamine formation could be dependent on the pH of the digestive system, eating and drinking habits, and the concentration of nitrite, tannins, and nitrosatable amines in the system.

- 6117 PROTECTION BY 1,1,1-TRICHLORO-2,2-BIS(p-CHLOROPHENYL)ETHANE (DDT) AGAINST MAMMARY TUMORS AND LEUKEMIA DURING PROLONGED FEEDING OF 7,12-DIMETHYLBENZ[a]ANTHRACENE TO FEMALE RATS. (Eng.) Silinskis, K. C. (Dept. Biology, Univ. Windsor, Windsor, Ontario, Canada N9B 3P4); Okey, A. B.* *J. Natl. Cancer Inst.* 55(3):653-657; 1975.

The effect of treatment with pesticides on the induction of mammary tumors and leukemia during prolonged oral administration of 7,12-dimethylbenz(a)anthracene (DMBA) was investigated. Female Sprague-Dawley rats, 36 days old, were pretreated for two weeks either with 100 ppm 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) or 250 ppm S-(1,2-dicarbethoxyethyl)0,0-dimethyldithiophosphate (Malathion) in the diet. From day 50 they were given, *via* stomach tube, 21 consecutive daily doses of 0.714 mg DMBA. Pesticide diets and observation of the animals for mammary tumors continued until necropsy, 230 days after the start of DMBA administration. DDT-treated rats had a significantly lower mammary tumor incidence, prolonged tumor latency period, and fewer tumors per rat than did the control group. Animals given Malathion had a higher mammary tumor incidence, shortened latency period, more tumors per rat, and more actively growing tumors than did the control group (DMBA only). Leukemia incidence in rats surviving to necropsy (230 days after the start of DMBA administration) was 11 out of 20 for control, 2 out of 29 for DDT, and 8 out of 12 for Malathion-treated rats. Leukemia was primarily myelogenous. The authors suggest that DDT may inhibit DMBA-induced mammary tumors and leukemia by stimulating hepatic metabolism and excretion of DMBA so that less carcinogen is available to peripheral tissues. Malathion may potentiate DMBA induction of mammary tumors and leukemia by inhibiting the same enzyme systems induced by DDT.

- 6118 BLASTOGENIC ACTIVITY OF p-HYDROXYPHENYL-LACTIC ACID IN MICE. (Eng.) Rauschenbach, M. O. (Inst. Exp. Clin. Oncol., Moscow, USSR); Zharova, E. I.; Sergeeva, T. I.; Ivanova, V. D.; Probatova, N. A. *Cancer Res.* 35(3):577-585; 1975.

Using C57BL/6 and CC57BR mice, the incidence of neoplasms was recorded in control mice and compared with that in mice receiving p-hydroxyphenyllactic acid (2.5 mg, twice weekly, total dose 42 mg, sc) or phenyllactic acid (2.5 mg twice weekly, total dose 50 mg,

- sc). The incidence of neoplastic development was 15% and 38% in control C57BL/6 and CC57BR mice. resp., 45% in CC57BR mice receiving phenyllactic acid, and 64% and 82% in C57BL/6 and CC57BR mice, resp., receiving *p*-hydroxyphenyllactic acid. Phenyllactic acid was not considered carcinogenic since the histogenic profile of the induced tumors was not significantly different from the control animals. Leukemias were the most common form of neoplasm in the animals receiving *p*-hydroxyphenyllactic acid (47/54 and 43/61 in the two strains), and of the leukemia, reticulosarcomatosis and lymphosarcomatosis were the most common forms. Other tumors included adenomas, hepatomas, and vascular tissue tumors, and there was a variety of benign and malignant tumors and precancerous lesions of the urinary bladder. It is concluded that *p*-hydroxyphenyllactic acid is one of the end factors of endogenic carcinogenesis induced by tryptophan metabolites.
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- 6178 CARCINOGENIC MECHANISMS OF 4-NITROQUINOLINE 1-OXIDE AND RELATED COMPOUNDS. (Eng.) Sugimura, T. (Natl. Cancer Res. Inst., Chuo-ku, Tokyo, Japan); Nagao, M.; Takeuchi, M.; Yahagi, T.; Hara, K.; Matsushima, T. *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Mucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 15-19.
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- 6180 BINDING OF CARCINOGENS TO NUCLEIC ACIDS AND PROTEINS. (Eng.) Kuroki, T. (Inst. Medical Science, Univ. Tokyo, Tokyo, Japan). *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 30-35.
- 6181 MECHANISMS OF DNA REPAIR IN MAMMALIAN CELLS AFTER ALKYLATING AGENTS. (Eng.) Fox, B. W. (Christie Hosp. and Holt Radium Inst., Withington, Manchester, U.K.). *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 153-156.
- 6182 DNA DAMAGE AND REPAIR IN VARIOUS ORGANS OF THE RAT INDUCED BY ALKYLATING CARCINOGENS [abstract]. (Eng.) Cox, R. (Veterans Administration Hosp., Memphis, Tenn.). *IRCS Med. Sci.* 3(10/Suppl.): 20; 1975.
- 6183 METHYLMERCURY: EFFECT ON ONCOGENIC AND NONONCOGENIC VIRUSES IN MICE. (Eng.) Koller, L. D. (Dept. Veterinary Medicine, Oregon State Univ., Corvallis, Oreg.). *Am. J. Vet. Res.* 36(10): 1501-1504; 1975.
- 6184 SYNTHESIS OF SOME BENZODIPYRONES, POTENTIAL PHOTOCHEMICAL DNA CROSSLINKING AGENTS. (Eng.) Marx, J. N. (Dept. Chem., Texas Tech. Univ., Lubbock); Song, P.-S.; Chui, P. K. *J. Heterocycl. Chem.* 12(2):417-419; 1975.
- 6185 SYNTHESIS OF SOME NITROSAMINOPURINE AND HYDROXYAMINOPURINE DERIVATIVES (1). (Eng.) Giner-Sorolla, A. (Mem. Sloan-Kettering Cancer Cent.,

New York, N.Y. 10021); Taracido, V. R. *J. Heterocycl. Chem.* 12(2):405-406; 1975.

6186 THE EFFECT OF REPRODUCTION AND LACTATION ON THE ONSET OF LATENT CHRONIC BERYLLIUM DISEASE. (Eng.) Clary, J. J. (Toxicology Branch, Natl. Inst. Occupational Safety Health, Cincinnati, Ohio 45202); Bland, L. S.; Stokinger, H. E. *Toxicol. Appl. Pharmacol.* 33(2):214-221; 1975.

6187 FURTHER STUDIES ON THE EFFECT OF CADMIUM ON THE PROSTATE GLAND. I. ABSENCE OF PROSTATIC CHANGES IN RATS GIVEN ORAL CADMIUM SULPHATE FOR TWO YEARS. (Eng.) Levy, L. S. (Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England); Clack, J. *Ann. Occup. Hyg.* 17(3/4):205-211; 1975.

6188 FURTHER STUDIES ON THE EFFECT OF CADMIUM ON THE PROSTATE GLAND. II. ABSENCE OF PROSTATIC CHANGES IN MICE GIVEN ORAL CADMIUM SULPHATE FOR EIGHTEEN MONTHS. (Eng.) Levy, L. S. (Inst. Cancer Res., Pollards Wood Res. Station, Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England); Clack, J.; Roe, F. J. C. *Ann. Occup. Hyg.* 17(3/4):213-220; 1975.

6189 EFFECT OF LOW DIETARY CALCIUM ON CHRONIC CADMIUM TOXICITY IN RATS. (Eng.) Washko, P. W. (Dept. Nutrition, Cook Coll., Rutgers Univ., New Brunswick, N.J. 08903); Cousins*, R. J. *Nutr. Rep. Int.* 11(2):113-127; 1975.

6190 EFFECTS OF MANGANESE ON TUMORIGENESIS AND METABOLISM OF NICKEL SUBSULFIDE [abstract]. (Eng.) Sunderman, F. W., Jr. (Univ. Connecticut Health Cent., Farmington, Conn.); Lau, T.; Minghetti, P. F.; Maenza, R.; Becker, N.; Onkelinx, C.; Goldblatt, P. *Proc. Am. Assoc. Cancer Res.* 16:139; 1975.

6191 A COHORT STUDY OF BRONCHIAL CARCINOMAS IN WORKERS PRODUCING CHROMATE PIGMENTS. (Eng.) Langard, S. (Inst. Occup. Health, Oslo, Norway); Norseth, T. *Br. J. Ind. Med.* 32(1):62-65; 1975.

6192 HEMATOGENOUS DISSEMINATION OF INGESTED POLY-VINYL CHLORIDE PARTICLES. (Eng.) Volheimer, G. (1 Berlin 92, Bayerischer Platz 9, Berlin, Germany). *Ann. N.Y. Acad. Sci.* 246:164-171; 1975.

6193 *IN VIVO* AND *IN VITRO* EFFECTS OF CIGARETTE SMOKE CONDENSATE FRACTIONS [abstract]. (Eng.) Kouri, R. (Microbiol. Assoc., Bethesda, Md.); Whitmire, C.; Benedict, W. *Proc. Am. Assoc. Cancer Res.* 16:173; 1975.

6194 COALWORKER'S PNEUMOCONIOSIS AND CARCINOMA OF THE LUNG. (Eng.) Mooney, F. S. (St. Helens Hosp., Marshalls Cross Road, St. Helens, Lancashire, England). *Lancet* 1(7903):390; 1975.

6195 PLASMA MEMBRANE AND TUMOR PROMOTER EFFECTS ON 3T3 CELL RNA SYNTHESIS [abstract]. (Eng.) Sivak, A. (Inst. Environ. Med., New York Univ. Med. Cent., N.Y.); Mossman, B. T. *Proc. Am. Assoc. Cancer Res.* 16:104; 1975.

See also:

* (Rev): 6001, 6002, 6003, 6004, 6006, 6007, 6008, 6009, 6009, 6010, 6011, 6012, 6013, 6014, 6015, 6016, 6018, 6021, 6024, 6038, 6039, 6040, 6041, 6042, 6043, 6044, 6046, 6069

* (Phys): 6211, 6216, 6217

* (Viral): 6236, 6267

* (Immun): 6287, 6298, 6338, 6339, 6343

* (Path): 6449

* (Epid-Biom): 6491, 6493, 6496, 6497, 6505, 6508

- 6196 EFFECT OF IRRADIATION ON THE PHOSPHORYLATION OF THE NUCLEAR PROTEINS OF THE LIVER AND THYMUS OF RATS. (Rus.) Umanskii, S. R. (Inst. Biological Physics, U.S.S.R. Acad. Sci., Pushchino, U.S.S.R.); Zotova, R. N.; Tokarskaia, V. I. *Radio-biologiya* 15(4):526-530; 1975.

The effect of *in vitro* irradiation on the nuclear phosphorylation and RNA synthesis in the rat liver and thymus was investigated. Low radiation doses (1 to 5 krad) resulted in the stimulation of protein phosphorylation of the nuclei and chromatin of the rat liver and thymus while high doses (10 to 20 krad) resulted in the inhibition of protein phosphorylation. No changes were observed in the dephosphorylation of chromatin protein in both organs or in the nuclear protein of the liver; however, the process was inhibited in the nuclear protein of the thymus under the action of gamma radiation. Phosphorylation of the nuclear proteins of the liver and thymus was increased by 37% and 15%, respectively, 15 min after *in vivo* exposure to a 1 krad dose. Two hr after exposure, a 10% increase in phosphorylation of the liver nuclei and a 23% decrease in phosphorylation of the thymus nuclei were observed. Fractionation of nuclear proteins revealed that *in vivo* radiation most enhanced phosphorylation of histones and had the least effect on nuclear sap proteins. The authors suggest that the protein phosphorylation in chromatin may depend on their relation to DNA.

- 6197 CELL KINETICS IN THE SKIN OF MICE ONE YEAR AFTER IRRADIATION WITH CYCLOTRON-ACCELERATED HELIUM IONS. (Eng.) Leith, J. T. (Lawrence Berkeley Lab., Univ. California, Berkeley, Calif.); Schilling, W. A.; Welch, G. P.; Tobias, C. A. *Cell Cycle in Malignant Immunology, Proc. Annu. Hanford Biol. Symp.*, 13th. Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 211-223.

The cell kinetics of the dorsal skin of the male CD-1 mouse was studied one year after irradiation with low-energy helium ions. Labeled mitoses curves were obtained by injecting the mice ip with 1 μ Ci 3 H-thymidine, keeping the mice on a 12-hr light-dark cycle, and analyzing various tissue samples at different times postinjection. The curves for dose levels of 75-2,000 rads indicated that the lowest dose at which definite disturbance in epidermal cell kinetics can be found is 1,200 rads. At this dose level and higher levels, the epidermis was characterized morphologically by the presence of a persistent hyperplastic epithelium. This acanthotic epidermis was associated with an increased duration of the G₁ phase of the cell cycle, a slower turnover time, and a greater number of cells with the ability to synthesize DNA per unit length of epidermis. The reason for the alteration in tissue organization is unknown, but two possibilities, i.e., damage to dermal structures and interference with normal growth-regulation processes, are discussed.

- 6198 THE PHOTOCARCINOGENICITY OF ANTHRACENE: PHOTOCHEMICAL BINDING TO DEOXYRIBONUCLEIC ACID IN TISSUE CULTURE. (Eng.) Blackburn, G. M.

(Dept. of Chemistry, Univ. of Sheffield, Sheffield S3 7HF, U.K.); Taussig, P. E. *Biochem. J.* 149(1): 289-291, 1975.

The influence of long-wavelength UV light on the interaction of anthracene with high-molecular weight DNA in mammalian tissue cultures was investigated. Monkey kidney epithelial and human skin epithelial cells were irradiated (365 nm for 24 hr), either immediately or after a dark incubation period. DNA was immediately harvested, hydrolyzed or examined by gel filtration. The DNA-hydrocarbon photoproduct was characterized by alkaline-sucrose-density gradient centrifugation (ASDGC). The specific radioactivity for the 14 C-labeled DNA-hydrocarbon indicated an association in excess of one hydrocarbon molecule per 10³ bases. The binding increased over 2-fold if the same irradiation dose was applied in 4-hr pulses. Lysed DNA cells applied to ASDGC after 4.5 hr incubation in the dark with hydrocarbon and two hours irradiation showed a molecular weight of 10⁵. The anthracene 14 C-labeled compound sedimented in coincidence with 3 H, except at the top of the gradient. Cells incubated in the dark for six hours with anthracene and without irradiation showed about 5% of this amount of 14 C in association with the DNA peak. Similar, but not linear, patterns were obtained with exposures of 15 min or 24 hr. However, the quantitative uptake of anthracene had not proven sufficiently reproducible to sustain accurate analysis of a dose-binding relationship, even though there was a decrease in viability with increased UV exposure.

- 6199 THE INDUCTION OF POLYKARYOCYTES BY VARIOUS FIBROUS DUSTS AND THEIR INHIBITION BY DRUGS IN RATS. (Eng.) Sethi, S. (Hygiene-Institut der Universität, 6300 Giessen, Friedrichstr. 16, West Germany); Beck, E. G.; Manojlovic, N. *Ann. Occup. Hyg.* 18(2):173-177; 1975.

U.I.C.C. chrysotile, glass fibers, and fibrous quartz, respectively, were administered ip to three groups of 24 female Wistar rats using the cover slip method. The animals were sacrificed at 24-hr intervals and the cover slips prepared for phase contrast and interference microscopy. On the first day, mononuclear dendritic and epithelioid macrophages were observed, which had phagocytosed fibrous material and deposited it perinuclearly in lysosomes. Between the fourth and fifty days, polykaryocytes appeared showing variable sizes and secondary integration of mononuclear cells. Giant cell morphology and mode of development were independent of the type of fiber administered. Control animals that had received Doerentrupper quartz, powdered glass, or physiological saline, showed only mononuclear cellular reaction during eight days of the experiment. Animals that received U.I.C.C. crocidolite were treated with meprobamate and procaine hydrochloride on the third to the fifth day. In this case, no polykaryocytes were found. The mechanism of polykaryocyte induction and the influence of the drugs as regards inhibition of polykaryocyte development are discussed.

- 6200 FAILURE OF ANAEMIC STRESS TO EVOKE LEUKAEMIA IN X-IRRADIATED RATS. (Eng.) Myers, D. K. (Chalk River Nuclear Lab., Chalk River,

Ontario, Canada). *Int. J. Radiat. Biol.* 28(2):177-180; 1975.

The possible role of anemic stress in inducing leukemia was investigated in X-irradiated black-hooded Collip rats. One hundred male and 100 female 5-wk-old rats were exposed to 330 R whole-body X-irradiation, causing no immediate deaths. Fifty received no further treatment; the rest were bled by cardiac puncture (removing a volume of blood equal to 2% of the body weight twice at a 24-hr interval. This procedure produced 40% mortality. The surviving animals were killed when death seemed imminent or when they reached the age of 16 mo. At various times during the course of three years, other groups of rats were exposed to different X-ray treatments. The number of 5-wk-old rats exposed to a single X-ray dose were: (a) 38 at 55 R, (b) 33 at 165 R, and (c) 50 at 495 R. Further groups of 5- and 10-wk-old rats were exposed to two doses of 330 R (40 rats); three doses of 165 R at 5, 8, and 10 wk (47); or five doses of 165 R at intervals of 8 or 9 days (63). Exposure of Collip rats to 330 R X-irradiation alone produced a slight increase in the incidence of fatal lymphatic disorders, which was not increased significantly by postirradiation bleeding. Most of the animals at risk survived the full period of observation. The incidence of fatal lymphatic disorders and of mammary tumors increased roughly linearly with radiation dose; there was no indication that repeated doses were much more or less effective than a single dose in inducing tumors. The incidence of skin tumors appeared to be related to radiation dose by a sigmoidal curve. These tumors were seen only in the males, mainly in the dorsal area, where the incidence reached high values. Animals exposed to 660-925 R total dose developed an average of 4-5 skin tumors per surviving male at 65 wk. The present data agree with previously published reports and indicate that extensive blood loss does not trigger the development of a high incidence of fatal leukemias in irradiated rats. There was no indication that a second exposure to a given dose of X-irradiation would increase tumor incidence by more than double the effect of the first exposure to that particular dose.

- 6201 MODIFICATIONS OF THE PARAMETERS OF MITOCHONDRIAL RESPIRATION AND OF CERTAIN NUCLEOTIDE LEVELS IN RAT HEPATOCYTES AFTER *IN VIVO* CONTAMINATION WITH PLUTONIUM (^{239}Pu) CITRATE. (Fre.) Pepin, G. (Laboratoire de Toxicologie, INSERM U 122, UER Hygiene et Protection de l'Homme et de son Environnement, Univ. Paris-Sud, 92290 Chateaufort-Malabry, France); Pasquier, C.; Vallee, C.; Duprey, F.; Boudene, C. *C. R. Acad. Sci. [D]* (Paris) 280(1):141-144; 1975.

Alterations in liver mitochondria of rats exposed to plutonium are examined. Solutions of plutonium citrate, 50 $\mu\text{Ci/kg}$ to 120 $\mu\text{Ci/kg}$, were injected iv into 242 rats. Mitochondrial oxidative-phosphorylation was followed on a Gilson GME oxygraph. In order to locate the site in the cell respiration chain where Pu exerts its toxic effect, the ADP/O ratio of the contaminated mitochondria was determined on three substrates: succinic acid, a combination

of pyruvic and malic acids, and glutamic acid. On the seventh day after Pu injection, O_2 consumption decreased 20.7% in mitochondria and 36.6% in whole liver cells. Results were nearly identical for all three substrates. Mitochondrial nucleotides were separated by chromatography on ion exchange resins and the eluant was read by UV. On the 11th day after contamination, the levels of AMP, ADP, ATP, FMN, and GTP decreased 70-119% whereas NAD and NADP increased 31% and 24%, respectively. Total mitochondrial protein decreased on the seventh day after dosage with Pu. Acute intoxication of the liver by a soluble form of monomeric Pu does not interfere with cellular respiration or the mechanisms of oxidative phosphorylation. The fall in ATP levels can explain the observed decrease in mitochondrial and cellular protein and may be responsible for the death of the animal.

- 6202 DISTRIBUTION OF ^{239}Pu IN MALE CBA MICE AFTER INTRAVENOUS AND INTRAPERITONEAL INJECTION [letter to editor]. (Eng.) Green, D. (Medical Res. Council, Radiobiology Unit, Harwell, Didcot, Oxon., OX11 0RD, England); Howells, G. R.; Humphreys, E. R. *Health Phys.* 29(5):798-799; 1975.
- 6203 DRAFT GENERIC ENVIRONMENTAL STATEMENT ON THE WIDE-SCALE USE OF PLUTONIUM POWERED CARDIAC PACEMAKERS. (Eng.) Anonymous. (Atomic Energy Commission, Washington, D.C.); 202 pp., 1975. [available through National Technical Information Services, Washington, D.C. Document No. TID-26718].
- 6204 INFLUENCE OF AGE ON THE TUMORIGENICITY OF PLUTONIUM-239 IN RATS [abstract]. (Eng.) Zwicker, G. M. (Battelle Pac. Northwest Lab., Richland, Wash.); Mahlum, D. D.; Sikov, M. R. *Proc. Am. Assoc. Cancer Res.* 16:161; 1975.
- 6205 THE TOXICITY OF PLUTONIUM. (Eng.) Day, M. J. (No affiliation given). *Br. J. Ind. Med.* 32(3):253; 1975.
- 6206 EPIDERMAL HYPERPLASIA INDUCED BY ULTRAVIOLET RADIATION; ERROR AND UNCERTAINTY OF MEASUREMENT. (Eng.) Blum, H. F. (Temple Univ. Health Sci. Cent., Philadelphia, Pa.); McVaugh, J.; Ward, M.; Bush, H. L., Jr. *Photochem. Photobiol.* 21(4):255-260; 1975.
- 6207 SUPPRESSION OF ULTRAVIOLET LIGHT-INDUCED TUMOR FORMATION BY DIETARY ANTIOXIDANTS. (Eng.) Black, H. S. (Baylor Coll. Medicine, Houston, Tex. 77025); Chan, J. T. *J. Invest. Dermatol.* 65(4):412-414; 1975.
- 6208 EFFECT OF EXCISION AND POST-REPLICATION DNA REPAIR ON THE CYTOTOXICITY AND MUTAGENICITY OF UV IN HUMAN SKIN FIBROBLASTS [abstract]. (Eng.) Maher, V. M. (Michigan Cancer Found., Detroit); Birch, N.; Mittlstat, M.; Otto, J.; Ouellette, L.; Schnur, T.; McCormick, J. J. *Proc. Am. Assoc. Cancer Res.* 16:158; 1975.

- 6209 ULTRA VIOLET CARCINOGENESIS [abstract]. (Eng.) Rosen, P. (Oak Ridge Natl. Lab., Tenn.) *Biophys. J.* 15(2):194a; 1975.
- 6210 ON THE MECHANISM OF ULTRAVIOLET RADIATION ADAPTOGENIC ACTION. (Rus.) Zabalueva, A. P. (A. N. Sysin Inst. of General and Communal Hygiene, Moscow, U.S.S.R.); Prokopenko, Iu. I.; Dantsig, N. M. *Vestn. Akad. Nauk SSSR* (3):23-26; 1975.
- 6211 INTERVAL EFFECT OF BETA IRRADIATION AND SUBSEQUENT 4NQO PAINTING ON SKIN TUMOR INDUCTION IN MICE [abstract]. (Eng.) Hoshino, H. (Natl. Cancer Center Res. Inst., Tokyo, Japan); Tanooka, H. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 44.
- 6212 ROLE OF PROLACTIN IN RADIATION-INDUCED MAMMARY CARCINOGENESIS IN RATS [abstract]. (Eng.) Ito, A. (Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan); Nakano, M.; Kodama, Y.; Yokoro, K. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 41.
- 6213 EFFECT OF LEUPEPTIN IN THE INDUCTION OF RADIATION-INDUCED THYMIC LYMPHOMA IN C57BL/6J MICE [abstract]. (Jpn.) Kasuga, T. (Natl. Inst. Radiology Sci., Chiba, Japan); Noda, Y.; Furuse, T.; Terasima, T. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 40.
- 6214 INDUCTION OF SALIVARY GLAND TUMORS IN RATS BY X-RAY IRRADIATION (2) [abstract]. (Jpn.) Takeichi, N. (Res. Inst. Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan); Hirose, F. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 38.
- 6215 INDUCTION OF RECTAL CARCINOMA BY LOCAL IRRADIATION WITH DIVIDED DOSES OF X-RAYS IN ICR MICE [abstract]. (Jpn.) Hirose, F. (Res. Inst. Nuclear Medicine Biology, Hiroshima Univ., Hiroshima, Japan); Takizawa, S.; Watanabe, H.; Takeichi, N.; Inoue, S.; Naito, Y. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 15.
- 6216 INHIBITION OF X-IRRADIATION INDUCED MAMMARY TUMORIGENESIS BY 17 β -ESTRADIOL [abstract]. (Eng.) Bogden, A. E. (Mason Res. Inst., Worcester, Mass.); Cobb, W. R.; Cate, C. C.; Kuo, E. Y. H.; Alex, S. A. *Proc. Am. Assoc. Cancer Res.* 16:56; 1975.
- 6217 *IN VITRO* TRANSFORMATION OF S. HAMSTER CELLS BY UV IRRADIATION IS ENHANCED BY X-IRRADIATION AND UNAFFECTED BY CHEMICAL CARCINOGENS [abstract]. (Eng.) DiPaolo, J. A. (Natl. Cancer Inst., Bethesda, Md.); Donovan, P. J. *Proc. Am. Assoc. Cancer Res.* 16:75; 1975.
- 6218 BASE MODIFICATION IN DNA BY CANCER INDUCING AGENTS. X-IRRADIATION [abstract]. (Eng.) Daoud, A. H. (Univ. Texas Syst. Cancer Cent., Houston, Tex.); Griffin, A. C. *Proc. Am. Assoc. Cancer Res.* 16:159; 1975.
- See also:
- * (Rev): 6016, 6017, 6018, 6056
 - * (Chem): 6075, 6129, 6133
 - * (Viral): 6275
 - * (Epid-Biom): 6498, 6501, 6502

VIRAL CARCINOGENESIS

- 6219 ANALYSIS OF ONCORNAVIRUS RNA SUBUNITS BY ELECTRON MICROSCOPY. (Eng.) Heine, U. I. (Natl. Cancer Inst., Bethesda, Md. 20014); Weber, G. H.; Cottler-Fox, M.; Layard, M. W.; Stephenson, M. L.; Zemecnik, P. C. *Proc. Natl. Acad. Sci. U.S.A.* 72(9):3716-3720; 1975.

Subunits of oncornavirus (avian myeloblastosis virus) RNA were isolated from purified 60-70S viral RNA by heat dissociation. Molecules sedimenting at 35S, assumed to be the major component of the viral genome, were visualized in the electron microscope and their lengths were statistically analyzed. The results indicate a rather heterogeneous population of molecules with five distinct, reproducible size groups, an observation that excludes the assumption of random degradation of the genome. The five molecule groups ranged from 0.3-2.0 μ m in length, representing molecular wt between 0.5×10^5 (16S) and 2.0×10^6 (30S). In addition, molecules of 28 and 18S RNA, always present in oncornavirus RNA preparations, were examined with the same method. A large number of molecules in the 28S fraction exhibited secondary structures similar to those characteristic for 28S ribosomal RNA. It is suggested that the production of RNA molecules of distinct length could occur through preferential cleavage at single-stranded exposed regions of the viral genome. Alternatively, proteins binding to the viral nucleic acids may protect and stabilize the genome only in certain areas; unprotected stretches at certain intervals would make the molecule accessible to cleavage.

- 6220 DETECTION OF ADENOVIRUS TYPE 12 GENOME IN CELLS OF SARCOMAS INDUCED BY THIS VIRUS IN HAMSTERS. (Rus.) Ageenko, A. I. (The P. A. Gertsen Res. Inst. Oncology, Moscow, USSR.); Chutkov, N. A. *Vopr. Onkol.* 21(9):62-65; 1975.

A comparative study was made of the frequency of activation of viral genome and the level of their expression in the sarcoma cells of hamsters induced with human adenovirus type 12 (A-12), in human embryo kidney cells, and in hamster embryo kidney cells. Sarcomas were induced in newly born hamsters by two sc injections of A-12; in 85 to 90% of the hamsters, the tumors appeared one month after injection. Serotyping of adenoviruses was accomplished by the neutralization of the cytopathic reaction. Adenovirus type 12 was used as the viral antigen. The cells of primarily-induced sarcomas persistently produced an infective form of A-12. Virus-neutralizing antibodies and antibodies to the T-antigen of tumors were detected in the sera of sarcoma-bearing hamsters. The presence of the T-antigen sarcoma A-12 was demonstrated by immunofluorescence, as well as by the absence of the specific luminescence of the surface membranes of A-12 sarcoma cells obtained from pulmonary micrometastases (A-12 MML). The presence of antibodies to the adeno-virus in the blood of tumor-bearing hamsters indicates that at least part of these tumors is virogenetic. Intact virus was not revealed from sarcomas A-12 MML; however, the presence of the virus genome was corroborated by the synthesis of T-antigens in the cells of all tumors

and the presence of viral and T-antibodies in the serum of some animals. The authors conclude that this experimental technique provides a more stable and earlier discharge of the infectious virus. The use of various tumor types demonstrates the different levels of repression of virus genomes.

- 6221 ASSOCIATION OF ENDONUCLEASE ACTIVITY WITH SEROTYPES BELONGING TO THE THREE SUBGROUPS OF HUMAN ADENOVIRUSES. (Eng.) Marusyk, R. G. (Dept. Medical Bacteriology, Univ. Alberta, Edmonton, Alberta T6G 2E1, Canada); Morgan, A. R.; Wadell, G. *J. Virol.* 16(2):456-458; 1975.

An ethidium bromide fluorimetric assay was used to detect the endonuclease activity associated with serotypes belonging to the three subgroups of human adenoviruses. Adenovirus serotypes 2, 3, 5, 9, 12, 15, and 16 were cultivated in KB cells or HeLa cells and released from degenerating cell cultures by sodium deoxycholate treatment or by several cycles of freeze-thawing. Virus particles were separated by centrifugation on discontinuous CsCl gradients, followed by equilibrium centrifugation in CsCl. Virion-derived pentons were obtained by dialysis of highly purified virion vs distilled water. Excess pool pentons were isolated by anion exchange chromatography on DEAE-Sephadex combined with exclusion chromatography on spherical agarose. Dodecons were obtained by adsorption and elution of excess pool components to *Cercopithecus aethiops* or human O erythrocytes, followed by rate zonal centrifugation on linear sucrose gradients. Only virion-derived pentons, excess pool pentons, and dodecons displayed endonuclease activity, and only single-strand breaks in substrate DNA were detected. All assayed preparations of hexons, both virion-derived and from the excess pool, and core components were negative as were highly purified adenovirus virions. The authors conclude that these results confirm the presence of an endonuclease activity with human adenoviruses and substantiate the ubiquitous nature of the endonuclease activity within the adenovirus group.

- 6222 SITE ON THE RNA OF AN AVIAN SARCOMA VIRUS AT WHICH PRIMER IS BOUND. (Eng.) Taylor, J. M. (Fox Chase Cancer Center, Philadelphia, Pa. 19111); Illmensee, R. *J. Virol.* 16(3):553-558; 1975.

The location of the site on avian sarcoma virus RNA at which primer is bound was determined. Secondary cultures of [3 H]-uridine-labeled chicken cells were infected at low multiplicity with avian sarcoma virus, either strain B77 or a nontransforming derivative, td-B77. The 4S RNA primer in the 70S RNA complex was marked by a short oligodeoxynucleotide labeled with 32 P. The 70S RNA complex was then isolated by sedimentation, partially denatured by heating into 35S subunits, and applied to a 0.5 g column of oligo(dT)-cellulose. The resulting poly(A)-containing and poly(A)-deficient (failed to bind to the column) fractions were separately analyzed by sucrose density gradient sedimentation. The 3 H-labeled poly(A)-containing RNA fragments ranged in sedimentation values up to 35S. The majority of the short oligodeoxynucleotide-labeled 4S RNA bound to

these fragments was associated with large 29 to 35S species, suggesting that the majority of primer binding sites are located at or near the 5'-terminus of the 35S RNA. The 35S RNA fragments were then analyzed on gels of 2.1% polyacrylamide to obtain a better estimate of the location of the primer binding site with respect to the 5'-terminus. The size distribution of the poly(A)-containing RNA was such that 70% of the ^{32}P was associated with species that were larger than 90% of the modal size, assuming that this size represents intact RNA. There was a smaller but significant fraction (as high as 30%) of primer molecules bound to smaller species (about 20 to 30S). The authors conclude that *in vitro* transcription of the avian tumor virus RNA by RNA-directed DNA polymerase is initiated on a unique circular 4S RNA and that, at least for the majority of 35S RNA molecules, the primer is bound at a site close to the 5'-terminus.

- 6223 PROTEIN KINASE AND ITS REGULATORY EFFECT ON REVERSE TRANSCRIPTASE ACTIVITY OF ROUS SARCOMA VIRUS. (Eng.) Lee, S. G. (Abbott Lab., North Chicago, Ill. 60064); Miceli, M. V.; Jungmann, R. A.; Hung*, P. P. *Proc. Natl. Acad. Sci. USA* 72(8):2945-2949; 1975.

The effect of protein phosphokinase (EC 2.7.1.37; ATP:protein phosphotransferase) and phosphoprotein phosphatase (EC 3.1.3.16; phosphoprotein phosphohydrolase) on reverse transcriptase (RNA-dependent DNA nucleotidyltransferase) activity of Rous sarcoma virus (RSV) was studied. Protein kinase was purified from RSV (Schmidt-Ruppin subgroup D)-transformed chick embryo fibroblasts. The protein kinases preparation contained a form dependent on cyclic AMP and an independent form. Purified reverse transcriptase from RSV was preincubated with protein kinase and ATP under conditions allowing incorporation of phosphate into substrate protein. After the preincubation, reverse transcriptase activity was assayed in the presence of poly(rA)·oligo(dT) as template. A 2-5-fold increase of reverse transcriptase activity was found. Incubation of reverse transcriptase with heat-treated, inactive protein kinase and ATP had no effect on transcriptase activity. When the transcriptase preparation was incubated with protein kinase and $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ and subsequently purified, significant amounts of ^{32}P -labeled proteins were found in the fractions exhibiting reverse transcriptase activity, suggesting ^{32}P incorporation into transcriptase or transcriptase-associated proteins. A 20-60% decrease of reverse transcriptase activity was observed after incubation of reverse transcriptase with phosphatase. The results suggest that the reverse transcriptase activity of an oncogenic RNA virus may be determined by the degree of phosphorylation of the enzyme. Stimulation of DNA synthesis appears to be associated with increased phosphorylation of reverse transcriptase.

- 6224 QUANTITATIVE CYTOCHEMICAL DETECTION OF ENZYMES IN CELL CULTURES INFECTED WITH ROUS VIRUS. (Rus.) Kolodin, V. I. (N. N. Petrov Res. Inst. Oncology, Ministry Health, Leningrad, USSR); Kuznetsov, O. K. *Vopr. Onkol.* 21(9):65-72; 1975.

Quantitative changes in enzyme activity, excluding age-related reactions, were studied in a monolayer culture of chick embryo cells infected with Rous sarcoma virus strain Carr-Zilber C3H (dose of $10^{4.6}$ to 10^5 focus-forming units). In the early period after injection (1 to 7 days), a moderate increase in the activity index of glycolytic and tissue respiratory enzymes was observed, reflecting the onset of cell transformation. The activity level of hexokinase and lipoamide dehydrogenase (NADH) remained relatively low. The increase in glycolytic enzymes from the third day after infection was primarily due to the appearance of foci of transformation with a higher energetic tension than the surrounding monolayer. In the later post-infection period (13-27 days), all monolayer cells, except dystrophic elements with a minimal enzyme activity, had a high level of glycolytic and pentose cycle enzymes and a low level of citric acid cycle and tissue respiratory enzymes. The numerous cytoplasmic vacuoles forming under the action of the virus were hypertrophic lysosomes and phagolysosomes, with a very high index of acid phosphatase activity. These data confirm previous findings on the predominance of anaerobic and aerobic glycolysis in viral blastomogenesis. The observed changes in enzyme activity in the cells infected with Rous sarcoma virus were a phenotypic manifestation of malignant transformation and reflected some common characteristics of the tumor cells.

- 6225 FAILURE TO OBTAIN TRANSFECTION WITH XC MITOCHONDRIAL DNA. (Eng.) Svoboda, J. (Inst. Exp. Biol. Genet., Czechoslovak Acad. Sci., Prague); Hložánek, I.; Korb, J.; Mach, O. *Eur. J. Cancer* 11(4):247-250; 1975.

The transfecting activity of DNA obtained from mitochondria of XC virogenic rat cells transformed with the Prague strain of Rous sarcoma virus (RSV) was tested. Both mitochondrial DNA isolated with ethidium bromide, containing circular molecules, and total mitochondrial DNA were inefficient in transfecting sensitive chicken fibroblasts in spite of the fact that doses of mitochondrial DNA (0.17-28 μg) up to two orders higher than the minimum efficient dose of total XC DNA were used. These findings support the view that a DNA transcript of the RSV genome is not integrated in mitochondrial DNA.

- 6226 IMIDAZOLE IN ORGANS OF INBRED CHICKENS SELECTED FOR RESISTANCE OR SUSCEPTIBILITY TO LYMPHOID LEUKOSIS OR MAREK'S DISEASE. (Eng.) Miller, V. L. (Dep. Agric. Chem. Anim. Sci., West. Washington Res. Extension Cent., Puyallup); Bearse, G. E.; Csonka, E. *Poult. Sci.* 54(1):195-199; 1975.

The imidazole levels in the liver, kidney and blood in strains of chickens resistant and susceptible to lymphoid leukosis (LL) and Marek's Disease (MD) are reported. The following strains were used: 6, 7 and 15I from U.S.D.A. Regional Poultry Research Laboratory; strains C, K, and S from Cornell University; and strains R and S from Heisdorf and Nelson Farm. Total imidazole was determined on 1.0 ml aliquots of

1% tissue homogenates using the colorimetric analysis. There was no significant difference among strains, either for total liver imidazole (52.7 $\mu\text{M/g}$ tissue), or for total kidney imidazole (39.9 $\mu\text{M/g}$ tissue). The liver imidazole in R and S strains (0.75 and 0.78 $\mu\text{M/g}$, respectively) were significantly lower than in other strains. The kidney imidazole in the R and S strains (0.419 and 0.443 $\mu\text{M/g}$ tissue, respectively) were also significantly lower than in other strains. There was a greater difference among strains in blood imidazole values than that in liver or kidneys. When blood imidazole values were grouped according to susceptibility to LL or MD, the weighted-means of LL-resistant strains were significantly higher than the values of susceptible groups. The weighted-means of blood imidazole levels of MD-resistant or susceptible groups were not significantly different. The values presented for blood imidazole levels were generally ten times higher than previously reported, due to the greater specificity of the assay employed.

6227 HSV TYPE I AND II: CLINICAL VIEW.
(Jpn.) Kawara, T. (Depts. Obstetrics and Gynecology, Tokyo Univ., Japan). *Virus (Tokyo)* 24(1):102-105; 1974.

The frequency of appearance of anti-herpes simplex virus Type-2 (HSV-2)-antibodies in the blood of patients with cancer of the cervix was determined to investigate the relation between HSV-2 and cervical cancer. In addition, HSV was isolated from various cases of herpes infection and identified as to type. A formula for calculating the actual amount of anti-HSV-2 in the blood was devised to compensate for the problems associated with measuring anti-HSV-2 antibodies in the blood: the percentage of anti-HSV-1 that cross-neutralized HSV-2 was subtracted from the measured amount of anti-HSV-2 antibodies. Anti-HSV-2 was found more frequently in the blood of cervical cancer patients, aged 30 to 40 yr, than in the control group. However, with a 50 to 70-yr-old age group no difference was detected between patients and controls. Herpes infection of female genital organs can be acute or recurrent. In cases of acute infection, HSV was frequently isolated from the outer pubic region and from the cervical canal. In cases of recurrent infection, HSV was not isolated from the cervical canal. Acute infection was usually due to HSV-1, while recurrent infection was due to HSV-2. The author found that the biological method that is based on the size of the plaque each type forms in the infected cells was useful for distinguishing between HSV-1 and HSV-2.

6228 CERVICAL CARCINOGENESIS WITH HERPES SIMPLEX VIRUS, TYPE 2. (Eng.) Wentz, W. B. (Univ. Hosp. Cleveland, Cleveland, Ohio 44106); Reagan, J. W.; Heggie, A. D. *Obstet. Gynecol.* 46(2):117-121; 1975.

The association between herpes simplex virus-type 2 (HSV-2) and cervical cancer was investigated in C₃H mice by applying a formaldehyde-inactivated preparation of HSV-2 to the mouse vagina and cervix over an extended period (up to 88 wk). The histologic alter-

ations were compared to those previously reported for experiments using coal tar hydrocarbons in a similar model of chemical carcinogenesis. HSV-2 was prepared by inoculating HEp-2 cell cultures with HSV-2 from a genital isolate. The earliest cytologic alteration, detected after 15 wk of exposure, was dysplasia with marked nuclear enlargement of oval and polyhedral cells. After longer exposure, the presence of early infiltrative lesions was seen in the cytologic preparations and was confirmed by histologic examination. Of the 67 HSV-2-treated animals, 21 developed dysplasia and 4 developed dysplasia and early infiltrative cancer. Four virus-treated mice had no abnormality. Frank invasive cancer was found in 14 animals in the cervix and uterine horns but did not involve the mucosa of the vagina or cervix in every case. Histologically, the lesions appeared to be moderately well-differentiated adenocarcinomas. An adenocarcinoma of the uterus with coexisting dysplasia of the cervix was seen in 8 of 14 mice with invasive lesions. The mucosal lesions seen in the HSV-2 treated mice were similar to those associated with exposure to coal tar hydrocarbons.

6229 INDUCTION OF CELLULAR DNA SYNTHESIS BY A TEMPERATURE-SENSITIVE MUTANT OF HERPES SIMPLEX VIRUS TYPE 2. (Eng.) Yamanishi, K. (Res. Inst. for Microbial Diseases, Osaka Univ., Suita, Osaka, Japan); Ogino, T.; Takahashi, M. *Virology* 67(2):450-462; 1975.

A temperature-sensitive mutant(ts 4) of herpes simplex virus type 2 (HSV-2), having the ability to transform hamster embryo (HaE) cells at the nonpermissive temperature of 38.5 C, was investigated in several aspects. It was defective in thymidine kinase induction at both the permissive (34 C) and the nonpermissive temperatures and defective in viral DNA synthesis at the nonpermissive temperature. However, stimulation of chromosomal DNA synthesis was detected at 16-28 hr after infection at the nonpermissive temperature in HaE cells arrested with low serum concentration. DNA synthesis was estimated by the incorporation of [³H]thymidine or [³H]deoxycytidine into DNA, and differentiation of cellular from viral DNA was performed by buoyant density gradient centrifugation in CsCl or by DNA-DNA hybridization. By autoradiography with [³H]-TdR, it was found that the number of cells with grains in the nuclei increased in infected cultures at 16-28 hr after infection. Virus exposed to heat or UV light lost the ability to induce cellular DNA synthesis, indicating that active virus is responsible for stimulation of cellular DNA synthesis.

6230 PRESENCE OF A HERPES SIMPLEX VIRUS DNA FRAGMENT IN AN L CELL CLONE OBTAINED AFTER INFECTION WITH IRRADIATED HERPES SIMPLEX VIRUS 1. (Eng.) Kraiselburd, E. (Roche Inst. Molecular Biology, Nutley, N.J. 07110); Gage, L. P.; Weissbach, A. *J. Mol. Biol.* 97(4):533-542; 1975.

Herpes simplex virus DNA sequences were detected in a mouse cell line selected for thymidine kinase activity after infection of a parental L cell thymidine kinaseless strain with irradiated Herpes simplex virus type 1. One of these clones (no. 139) was

analyzed for the presence of the virus genome. Re-association kinetic analyses using iodinated virus DNA (60 hr at 75 C) established that there were five copies of a fragment comprising about 23% of the virus genome in each clone cell. This value could be an underestimate because reactions of sufficient duration and Herpes simplex virus DNA concentration to reassociate all the Herpes simplex virus probe DNA were not performed. Neither the parental thymidine kinaseless L cell line nor a revertant cell line obtained from the clone showed any detectable virus DNA-specific sequences. These results suggest that the thymidine kinase activity is probably encoded by a fragment of the viral genome integrated in the DNA of the clone 139 cells.

- 6231 CHARACTERISTICS OF CELL LINES DERIVED FROM HUMAN LEUKOCYTES TRANSFORMED BY DIFFERENT STRAINS OF EPSTEIN-BARR VIRUS. (Eng.) Katsuki, T. (Kumamoto Univ. Med. Sch., Japan); Hinuma, Y. *Int. J. Cancer* 15(2):203-210; 1975.

The effect of Epstein-Barr virus (EBV) on the properties of cell lines derived from transformed cells *in vitro* was studied after infection with different EBV strains. Human umbilical cord WBC from six different individuals were infected with the two virus strains derived from either the B95-8 marmoset cell line or QIMR-WIL cell line; 12 lymphoblastoid cell lines were established. Immunoglobulin production was assayed by direct immunofluorescent staining. EBV-associated nuclear antigen was determined by the anti-complement immunofluorescence test. The presence of EBV-associated early antigen, viral capsid antigen, and EBV-associated membrane antigen was also determined. All 12 cell lines showed a morphological lymphoblastoid nature for single cells. The maximum number of cells per milliliter was higher in all QIMR-WIL lines than in B95-8 lines up to 6 months after establishment. Up to four days post-inoculation, most cell clumps in the B95-8 lines had a ball form, and those in the QIMR-WIL lines had a flake form. All lines produced cytoplasmic IgM, IgG, and IgX, but not IgA and membrane-associated IgM and IgX but not IgG. The frequency of cells producing cytoplasmic IgM or IgG-chains was higher in all B95-8 lines, as were cells with membrane-bound IgX chains. All lines had the EBV-associated nuclear antigen in over 90% of cells. Virus infectivity was detected in culture fluid from five QIMR-WIL cell lines and in none of five B95-8 lines tested. A high titer of infectivity comparable to the original virus line was found in one of the five infectious QIMR-WIL derived lines. The data indicate that different strains of the Epstein-Barr virus may induce different transformations of cells.

- 6232 AMOUNTS OF EPSTEIN-BARR VIRUS DNA IN SOMATIC CELL HYBRIDS BETWEEN BURKITT LYMPHOMA-DERIVED CELL LINES. (Eng.) Anderson, M. (Dept. Tumor Biology, Karolinska Institutet, Stockholm 60, Sweden). *J. Virol.* 16(5):1345-1347; 1975.

The amounts of Epstein-Barr virus (EBV) DNA in somatic cell hybrids between human lymphoid cell lines were determined by nucleic acid hybridization. Seven hybrid clones were constructed between a surface-

adherent variant of the Raji cell line AGR3 (which contains 50-60 EBV genome equivalents per cell), and the Namalwa line (which has 3 ± 1 viral genome equivalents per cell). Although the hybrids were not induced to spontaneous virus production, all seven clones contained higher amounts of EBV DNA than the parental cell lines. The hybrids were close to tetraploid because they contained 88-90 chromosomes; the Namalwa parent has 45 chromosomes and the AGR3 parent has 48 chromosomes. The hybrid cells contained 100-180 EBV genome equivalents per tetraploid cell. Similar results were obtained with hybrids between Raji and BJA-B-1, and EBV-negative lymphoid cell line. The three hybrid clones investigated contained 200-270 EBV genome equivalents per tetraploid cell, which again exceeded the amount of viral DNA in the parent lines. One possible explanation for the results is that chromosomes containing EBV DNA were selectively retained and amplified in the hybrid cells. Another possibility is that the mechanisms that regulate the ratio of virus genomes to cellular DNA in the lymphoid cells were affected by the fusion of the cells. It appears unlikely that the hybrid cells were induced to an abortive lytic cycle, which would have initiated viral DNA replication.

- 6233 OCCURRENCE OF EPSTEIN-BARR VIRUS IN HUMAN LEUKOCYTE CULTURES. (Eng.) Gerber, P. (Food and Drug Administration, Bureau of Biologics, Div. Virology, 8800 Rockville Pike, Bethesda, Md. 20014). *In Vitro* 10(5/6):247-252; 1974.

The occurrence of the Epstein-Barr virus (EBV) in long-term human leukocyte cultures is reviewed. Most long-term human lymphoid cell lines, including those that appear to be "virus-free" contain the viral DNA and virus-specific nuclear antigens, and the role of EBV in converting mature lymphocytes from normal donors into rapidly dividing lymphoblasts with unlimited life span *in vitro* has been demonstrated. These cell lines contain several copies of the whole EBV genome in a repressed state, which can in some cases be activated by treatment with halogenated pyrimidines. There is no known documented case of the successful establishment of lymphoid cell lines from EBV-seronegative normal individuals. However, a few lymphoid cell lines which have recently been established from patients with acute lymphocytic leukemia or lymphoma are free of detectable EBV DNA and antigens. These cells may represent the malignant tissue of origin and exhibit the growth potential of the parent cells. However, each of the patients from whom these cell lines were derived had serologic evidence of previous EBV infection, and the unlimited life span of the cultured cell lines may be due to the presence of a fragment of EBV DNA forming less than 10% of the total DNA and therefore not detectable by current techniques. This fragment could code for proteins involved in the transformation process. The presence of endogenous EBV in most established human leukocyte cultures indicates a potential biohazard to laboratory workers. The use of vertical laminar-flow hoods and careful handling of these cultures is suggested. In addition, the interpretation of results of biological, biochemical, and

immunological studies employing lymphoid cell lines should take into account the presence of endogenous viral components.

- 6234 HELPER ACTIVITY FOR THE DEFECTIVE FRIEND LEUKEMIA VIRUS IN HUMAN MALIGNANT CELL CULTURES. (Eng.) Fjelde, A. (Roswell Park Memorial Inst., Buffalo, N.Y.). In: *Human Tumor Cells in Vitro* edited by Fogh, J. New York, Plenum Press, 1975, pp. 517-549.

Helper activity for the defective Friend leukemia virus was investigated in human malignant cell cultures. Human helper activity assays were performed on cell cultures of spleen bone marrow, and peripheral blood from patients with lymphoreticular diseases and in bone marrow cultures from patients with neuroblastoma. The tissue was minced in Eagle's minimum essential medium with 10% fetal calf serum and the cells centrifuged out immediately or cultured. The supernatant, used for the helper activity assay, was centrifuged at 75,000 g for 2 hr. The pellet was resuspended in phosphate-buffered saline and injected, iv (with the incomplete murine Friend leukemia virus) into genetically suitable mice. The number of foci in the spleens of these mice was compared with the number found in the spleens of mice injected with the incomplete virus alone. In addition to human helper activity, lymphomas showed reverse transcriptase and 70S RNA homologous with Rauscher leukemia virus and demonstrated heterophile antigen. A number of cell lines have been derived directly from human tissue showing helper activity and from such tissue cocultivated with normal human embryo cells; other human cell lines were treated with extracts showing helper activity and grew rapidly. Some of these cultures were examined for virus particles but none was detected. 3-Deazauridine, an inhibitor of RNA viruses, inhibited the helper activity of human malignant tissue extracts for the defective Friend spleen focus forming virus complex. The inhibition of activity was seen with tissues from a variety of malignancies, including neuroblastoma and several lymphomas, Hodgkin's disease, reticulum cell sarcoma, and lymphosarcoma. It is concluded that evidence of helper effect has been obtained from human malignant hematopoietic tissues and from neuroblastoma. It is also concluded that the medium used for the human helper activity studies furnished a suitable environment for the helper activity, which, as yet, has not been clearly defined.

- 6235 TRANSFER RNAs ASSOCIATED WITH THE 70S RNA OF AKR MURINE LEUKEMIA VIRUS. (Eng.) Waters, L. C. (Carcinogenesis Program, Biology Div., Oak Ridge Natl. Lab., Oak Ridge, Tenn. 37830). *Biochem. Biophys. Res. Commun.* 65(3):1130-1136; 1975.

The tRNA species associated with the 70S RNA of AKR murine leukemia virus grown in mouse embryo cells were studied. The viral 70S RNA was heated to 60 C after isolation, and the dissociated 4S fraction separated by sucrose gradient sedimentation. The 70S RNA was then reheated to 80 C. The nature of

the tRNA species removed after each stage of heating was established by aminoacylation with radiolabeled amino acids and subsequent use of an amino acid analyzer. A high content of proline tRNA (constituting 50-60% of the total identified tRNAs) in the 60-80 C 4S fractions, but not in the 60 C fractions, strongly indicated a major association between it and the viral 70S RNA. By analogy to avian viral systems (where tryptophan tRNA is the predominant species in the 60-80 C fraction), it is considered that proline tRNA may serve as a primer for reverse transcription of the murine leukemia virus RNA.

- 6236 EFFECT OF GLUCOCORTICOIDS ON ACTIVATION OF LEUKEMIA VIRUS IN AKR MOUSE EMBRYO CELLS. (Eng.) Ihle, J. N. (Oak Ridge Natl. Lab., Tenn.); Lane, S. E.; Kenney, F. T.; Farrelly, J. G. *Cancer Res.* 35(2):442-446; 1975.

The effect of glucocorticoids on activation and replication of leukemia virus in AKR mouse embryo cells was analyzed. Using AKR mouse embryo cells, passage 44, activation of endogenous AKR virus was assayed by immunofluorescent techniques. An affinity chromatography method was used to distinguish intracellular viral type reverse transcriptase from cellular DNA polynucleases. In preliminary experiments using immunofluorescent techniques to determine glucocorticoid effects of virus activation, an optimal concentration of 0.5-1 μ M hydrocortisone increased the number of cells scored as positive by 2 to 3-fold; there was no effect of hydrocortisone on incorporation of [3 H]leucine into the cellular proteins. Phase-specific action of hydrocortisone indicated that only when hydrocortisone was added during the second phase was virus protein synthesis enhanced; the results indicate that hydrocortisone does not affect formation of the activation intermediate, but modulates the extent of expression after activation. The effect of hydrocortisone on chronically infected AKR cells was to approximately double the virus yield. In contrast, no change was observed in intracellular reverse transcriptase activity. Studies on a dexamethasone-binding protein suggest the presence of a single class of receptor sites; the protein nature of such 4S receptors is indicated by the finding that the [3 H]dexamethasone complex is not sensitive to DNase or RNase, but completely destroyed by pronase. The observations suggest that the intracellular level of the structural virus proteins is probably increased by the hormone, and that the reverse transcriptase may be the limiting component for formation of complete virus.

- 6237 TRANSFECTION OF XC PLAQUES WITH DNA FROM MURINE LEUKEMIA VIRUS PRODUCER CELLS. (Eng.) Brunner, M. (Harvard Medical Sch., Boston, Mass. 02115). *Biochem. Biophys. Res. Commun.* 66(1):397-402; 1975.

Transfection of leukemia virus resulting in virus production was accomplished by treating murine NIH/3T3 cells with DNA (6 or 12 mg) extracted from Moloney leukemia virus-infected murine NIH/3T3 cells. Virus production was detected in a bioassay by XC plaque formation and in a biochemical assay for reverse transcriptase activity. Infection by DNA was suc-

cessful using the Calcium method, but not with the DEAE dextran method or with a high (60 mg) DNA concentration. XC plaques were observed as early as the first subculture of transfected NIH/3T3 cells. The ability to transfect murine leukemia virus information, along with the previously reported murine sarcoma virus transfection, may allow the study of interactions between replication (leukemia) and transformation (sarcoma) function in the murine virus system.

- 6238 PROPERTIES OF MOUSE LEUKEMIA VIRUSES. IX. ACTIVE AND PASSIVE IMMUNIZATION OF MICE AGAINST FRIEND LEUKEMIA WITH ISOLATED VIRAL GP₇₁ GLYCOPROTEIN AND ITS CORRESPONDING ANTISERUM. (Eng.) Hunsmann, G. (Forscherguppe Tumorimmunologie, Freiburg, Brsg., West Germany); Moennig, V.; Schafer, W. *Virology* 66(1):327-329; 1975.

Active and passive immunization of highly inbred mice (low leukemic STU strain) against virus-induced leukemia was attempted using isolated viral GP₇₁ glycoprotein (the major surface glycoprotein of Friend leukemia virus FLV) and its antiserum. For active immunization, vaccines were prepared by emulsifying GP₇₁ in complete or incomplete Freund adjuvants. Mice were inoculated with the vaccine at multiple sites at 12 wk of age, boosted 4 wk later, and challenged 1 wk after boosting by ip injection of a cell-free filtrate (0.2 ml) of an extract prepared from FLV-leukemic mouse spleens containing 14×10^3 PFU/0.2 ml. For passive immunization of mice, GP₇₁-specific antisera prepared in a rabbit and a goat were used. Groups of 10-wk-old mice were infected with FLV, in one experiment, they were inoculated im at days 3, 7, and 11 after infection with 0.4 ml anti-GP₇₁ rabbit serum and in the second experiment at days 7, 8, 10, 12, and 14 with 0.4 ml of anti-GP₇₁ goat serum. The immunizing effect of GP₇₁ was indicated by the finding that no plaque-forming units were detectable in pooled sera or in the spleens of mice inoculated with the highest GP₇₁ doses but found in appreciable amounts in the others. The minimal protective dose of GP₇₁ appeared to be rather high but corresponded approximately to that of purified fowl plaque virus hemagglutinin (25 µg) used in analogous experiments in young chickens. Treatment with GP₇₁ antiserum prevented the FLV-induced increase in spleen weight even when started 1 wk after infection. The authors suggest that immunization against murine C-type virus-induced leukemia can be achieved with a single well-defined viral component, which would minimize the danger of undesired side effects caused by genetic material and other viral components.

- 6239 EVOLUTION OF TYPE C VIRAL GENES: ORIGIN OF FELINE LEUKEMIA VIRUS. (Eng.) Benveniste, R. E. (Natl. Cancer Inst., Bethesda, Md. 20014); Sherr, C. J.; Todaro, G. J. *Science* 190(4217):886-888; 1975.

Studies are reviewed which show that reiterated gene sequences related to the RNA of feline leukemia virus (FeLV) are found not only in the cellular DNA of specific pathogen-free domestic cats (*Felis catus*) but also in the DNA of three closely related *Felis* species, the jungle cat, the sand cat, and

the European wildcat. More distant *Felis* species lack these genes, while the cellular DNA of rodents, and in particular that of rats, contains related virogenic sequences. The absence of such sequences in other Felidae and their presence in rodents suggest that FeLV-related genes were introduced into the *Felis* lineage after trans-species infection by a type C virus of rodent origin. This possibility is supported by immunologic studies showing that an antiserum to the reverse transcriptase of FeLV cross-reacts strongly with enzymes of endogenous rat type C viruses and less well with the polymerases of endogenous murine and hamster viruses. Like the reverse transcriptases, the p30 proteins of rodent, and particularly rat, type C viruses are immunologically related to each other and to FeLV, indicating their derivation from a common ancestor.

- 6240 LOCATION OF THE T4 GENE 32 PROTEIN BINDING SITE ON POLYOMA VIRUS DNA. (Eng.) Yaniv, M. (Departement de Biologie Molculaire, Institut Pasteur, 75015 Paris, France); Chestier, A.; Dauge, C.; Croissant, O. *FEBS Lett.* 57(2):126-129; 1975.

Because previous studies with Eco-R1 restriction endonuclease did not clearly establish the absolute location of the bacteriophage T4 gene 32 protein binding site on polyoma virus DNA, a search was made for another restriction enzyme that cleaves polyoma DNA in a unique site. This requirement was met by BamI endonuclease, isolated from *Bacillus Amyloliquefaciens*, which cleaves polyoma DNA at 0.58. Polyoma superhelical DNA was then treated with the T4 gene 32 protein and fixed with glutaraldehyde to obtain denaturation loops visualizable by electron microscopy. After dialysis, the DNA samples were treated with either Eco-R1 or BamI restriction enzymes, and the distance between the middle of the denaturation loops and the nearest Eco-R1 or BamI end was measured. Superhelical polyoma DNA could be alternatively denatured at either one of two A-T rich regions. The two major sites that bound gene 32 protein were in position 0.24 (0.34 on BamI) and 0.80 (0.22 on BamI). The frequency of loops in these sites was 42% and 29%, respectively, of the total loops observed. Minor binding sites were located in positions zero, 0.08, 0.45, and 0.59 of the polyoma physical map.

- 6241 DENATURATION MAP OF POLYOMA DNA. (Eng.) Lescure, B. (Institut Pasteur, Departement de Biologie Molculaire, 75015 Paris, France); Yaniv*, M. *J. Virology* 16(3):720-724; 1975.

A denaturation map of polyoma DNA that was established by electron microscopy was aligned with the established physical map of polyoma DNA. A reference point on circular polyoma DNA was produced using *Escherichia coli* restriction endonuclease (Eco R₁) to cleave it at a unique site. The linear molecules were partially denatured at pH 11 and spread for electron microscopy. All linear molecules of unit length showed a common structure: only one end was denatured. There were three major regions presumed rich in guanosine-cytosine base pairs (0.42, 0.71, and 0.90 to 1.00 fractional lengths from the denatured

end) and three minor native regions (0.09, 0.27, and 0.63). Four main regions presumed rich in adenosine-thymine base pairs were located at 0.0 to 0.07, 0.13 to 0.24, 0.52 to 0.58, and 0.78 to 0.86 from the left-hand end. To correlate the linear map with the established map of *Haemophilus parainfluenzae* Hpa II polyoma DNA fragments, the denaturation of fragments produced by cleavage with *Haemophilus influenzae* restriction enzymes II and III was studied (*Hin* II and III, respectively). The histogram of the major fragment from *Hin* II, III digestion correlated with the native end of the *Eco* R₁ linear DNA histogram, unambiguously defining the orientation of the denaturation map relative to the established map of Hpa fragments. Moreover, the results agreed with the order and base composition of polyoma DNA fragments obtained by digestion with Hpa II.

- 6242 THE UPTAKE OF ACTINOMYCIN D BY NORMAL AND VIRUS TRANSFORMED BHK21 HAMSTER CELLS. (Eng.) Williams, J. G. (Imp. Cancer Res. Fund Lab., London, England); Macpherson, I. A. *Exp. Cell Res.* 91(2):237-246; 1975.

The uptake of actinomycin-D (AMD) by the hamster cell line BHK 21, clone 13, and its polyoma virus-transformed derivative (BHK-PV) were compared. The intracellular AMD concentration was determined in subconfluent cultures of cells. Nuclei were then isolated by a non-ionic detergent cell disruption technique, and the RNA synthesis by the isolated nuclei and [³H]AMD binding by the isolated nuclei were assayed. The efflux of AMD from subconfluent cultures of BHK and BHK-PV cells was also determined, as was the recovery of RNA synthesis after AMD inhibition. At an AMD concentration of 0.01 µg/ml, AMD uptake by BHK-PV cells plateaued starting at about 3 hr of incubation, the internal AMD level at this point being 0.31 pM/µg DNA. Uptake by the BHK cells decreased over the course of incubation, but at all times, the BHK cells took up more AMD than the transformed cells. The intracellular AMD level at equilibrium was about 3.3-fold higher in the transformed cells. The BHK and BHK-PV cells did not differ in terms of the number of DNA binding sites for AMD or in the equilibrium constant for binding, the uptake into BHK-PV nuclei being consistently higher than the uptake into BHK nuclei. The incorporation of [³H]UTP by isolated nuclei was reduced in the presence of AMD, the sensitivity of BHK-PV nuclei being slightly greater than that of BHK nuclei. Cyclic AMP (cAMP) (0.2 mM) produced an approximate 2.5-fold increase in AMD uptake and a delay in equilibration in BHK-PV cells, the uptake into BHK cells being increased by only 1.2-fold. The efflux of AMD from BHK cells proceeded with the first order kinetics of a dissociation "reaction"; the transformed cells showed an approximately two-fold higher rate constant for AMD efflux. RNA synthesis recovery experiments showed that over the first 2 hr, BHK-PV cells recovered most of their [³H]uridine incorporation, the recovery occurring more quickly than in BHK cells. The results provide evidence for changes in plasma membrane function in the transformed cell.

- 6243 AMPLIFICATION OF A SPECIFIC REGION OF THE POLYOMA VIRUS GENOME. (Eng.) Griffin, B. E. (Imperial Cancer Res. Fund, PO Box 123, Lincoln's Inn Fields, London WC2A 3PX, UK); Fried, M. *Nature* 256(5514):175-179; 1975.

The sequences of polyoma D-50 and the relation of these sequences to those around the origin of replication were studied in wild-type polyoma DNA. Treatment of D-50 with HpaII produced one predominant partial digestion product, of length corresponding to about 17% of the wild-type genome. The results of fine-structure mapping with HaeIII and with depurination are consistent with the following composition for these DNAs: tandemly repeating 17% units containing all the sequences from polyoma HpaII-5 (wild-type A-3 strain) and some sequences from HpaII-3 and -4.

- 6244 ANTIGENIC CHARACTERISTICS OF HAMSTER CELLS TRANSFORMED BY A POLYOMA VIRUS. (Ita.) Iorio, A. M. (Cattedra di Virologia, Via del Giochetto, 06100 Perugia, Italy); Santoni, A.; Rivoecchi, P.; Campanile, F. *Boll. Ist. Sieroter. Milan* 54(1):31-35; 1975.

The presence of tumor specific transplantation antigens (TSTA) and surface antigens (S) was studied with the surface immunofluorescence technique in hamster cells transformed by a polyoma virus. Cells derived from a polyoma virus induced tumor (G-Py) and from PARA-adenovirus 7 induced tumor (PARA-7) were used. For the study of TSTA, 3- to 4-month-old Syrian hamsters were injected id, twice with polyoma virus, with nononcogenic doses of G-Py, or with oncogenic doses accompanied by successive removal of the tumors. These animals together with a group of control animals were then injected with 10⁴ G-Py. The appearance of tumors in the pretreated hamsters was slower than that in controls, and the number of animals in which tumors developed was lower. For the controls, four tumors developed between days 26 and 30, one on day 60, and one of the six hamsters was completely resistant. In the pretreated hamsters, five tumors developed between days 30 and 52; three other tumors appeared after 70 days and had limited development. Six out of 14 hamsters were completely resistant. In three of these, however, autopsy revealed traces of lung carcinoma with the same morphology as the tumors induced by sc injection of G-Py. Results for animals once injected with 10⁴ G-Py show that, independent of the presence, development, or absence of a tumor, the response was always positive. However, the sera were always negative for PARA-7 cell lines. Positive response was obtained in pretreated animals (also independent of the tumors). The same sera examined for PARA-7 cell lines were all negative. The authors conclude that TSTA and S are both present in the G-Py cell studied. However, the results are insufficient to state that both types of antigens represent the same entity and that there exists the possibility of the development of metastases in certain apparently immune animals.

- 6245 CHARACTERIZATION OF HUMAN PAPOVAVIRUS BK DNA. (Eng.) Howley, P. M. (Natl. Inst. Allergy Infect. Dis., Bethesda, Md.); Mullarkey,

M. F.; Takemoto, K. K.; Martin, M. A. *J. Virol.* 15(1):173-181; 1975.

The physical properties of BK virus DNA were further characterized, and the polynucleotide sequence homology between Simian virus 40 (SV40) and BK virus DNA was investigated. The DNA isolated from purified BK virions co-banded with SV40 DNA I in CsCl-ethidium bromide isopycnic gradients, confirming previous indications of a supercoiled configuration. Analysis of ^{32}P -labeled BKV DNA by electrophoresis yielded four discrete bands, indicating its heterogeneity. The largest band was designated BKV DNA (i); its mobility indicated a slightly smaller size than SV40 DNA. The remaining, more rapidly moving, migrating species were designated BKV DNA (ii, iii, and iv). A cytopathic effect was noted in cells infected with BKV DNA (i). In an infectivity assay of the various forms of BKV DNA, HEK cells were infected with BKV stock; only BKV DNA (i) was the predominant newly synthesized DNA species present, suggesting that it alone can replicate autonomously. In experiments on restriction endonuclease cleavage of BKV DNA, digestion of homogenous ^{32}P -labeled supercoiled BKV DNA (i) with R-Hind enzyme resulted in four cleavage products, ranging in size from 0.34×10^6 to 1.5×10^6 daltons. An attempt to localize the R-Eco RI cleavage site utilized successive cleavage of ^{32}P -labeled viral DNA with R-Eco RI and R-Hind restriction endonucleases; the two new cleavage products that appeared indicated the location of the R-Eco RI site within a R-Hind fragment. Nucleotide sequence homology between SV40 and BKV DNA was assessed through observation of the effect of unlabeled SV40 DNA on the kinetics of reassociation of ^{32}P -labeled BKV DNA; only a partial homology of 20-30% was revealed. It is suggested that genome heterogeneity is not an intrinsic property of the BVK, and that homology between BKV and SV40 DNA involves sequences located in the early region of the SV40 genome.

6246 ISOLATION OF FOAMY VIRUS FROM RHESUS, AFRICAN GREEN AND CYNOMOLGUS MONKEY LEUKOCYTES. (Eng.) Feldman, M. D. (Bureau Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, Md. 20014); Dunnick, N. R.; Barry*, D. W.; Parkman, P. D. *J. Med. Primatol.* 4(5):287-295; 1975.

The frequency of foamy virus (FV) occurrence in monkey WBC and some events occurring in natural and experimentally induced FV infection are presented. The monkeys studied included Indian rhesus monkey (*Macaca mulatta*), cynomolgus (*Macaca fascicularis*), and African green (*Cercopithecus aethiops*). Virus was recovered from peripheral blood WBC of 13 of the 32 rhesus and 7 of 7 cynomolgus monkeys, but found in only one of the six African green monkey WBC preparations. Leukocytes of adult rhesus monkeys born in the wild yielded more virus (12 of 25) than those of infant monkeys born in captivity (1 of 7). The numbers of animals possessing complement fixation (CF) antibodies correlated with the monkeys' places of origin. Of the monkeys caught in the jungle, all of the nine cynomolgus and 36 of the 40 adult rhesus monkeys had CF antibody for FV. In

contrast, of the monkeys born in captivity, only one of 12 African green and five of 16 infant rhesus monkeys tested possessed demonstrable CF antibody. Postmortem examination (at 14 and 16 wk) or 2 of 3 rhesus monkeys with experimentally induced FV (iv inoculation $10^{5.3}$ TCID₅₀ of FV type I) revealed FV in lymph node, spleen, salivary gland, lung, skeletal muscle, kidney, and liver tissue. FV was found in the heart of one of the two monkeys and in the brain of the second. None of the experimentally inoculated animals showed obvious signs of illness. It is suggested that the lower frequency of the virus in infant rhesus monkeys is related to a more limited contact with chronic virus excretors. The authors conclude that the high frequency of isolation of FV from peripherally circulating WBC of adult rhesus and cynomolgus monkeys indicates a marked tropism of FV for such cells. The widespread distribution of FV in many organs may be the result of residual WBC infected with FV in these tissues.

6247 MOLONEY SARCOMA VIRUS-INDUCED TUMORS IN ATHYMIC (NUDE) MICE: GROWTH PATTERN AND ANTIBODY RESPONSES. (Eng.) Davis, S. (Nat'l. Cancer Inst., Bethesda, Md.). *J. Nat'l. Cancer Inst.* 54(3):793-794; 1975.

Tumor growth and antibody production were evaluated in nude (*nu/nu*) mice and their heterozygous normal (*+/nu*) littermates after inoculation of Moloney sarcoma virus (MSV, 10^6 focus forming units/ml, im). Sarcoma-bearing nude mice developed progressively growing tumors, whereas, 53% of their normal counterparts showed tumor regressions. By indirect membrane fluorescence, significant amounts of IgG antibody to MSV could be detected in thymus-bearing but not in nude mice. The absence of IgG antibodies with MSV specificities in nude mice indicates that the antibody response to MSV antigens is T-cell dependent.

6248 MURINE SARCOMA VIRUS DEFECTIVENESS: VIRAL POLYMERASE EXPRESSION IN MURINE AND NON-MURINE HOST CELLS TRANSFORMED BY S+L- TYPE MURINE SARCOMA VIRUS. (Eng.) Peebles, P. T. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Gerwin, B. I.; Pageorge, A. G.; Smith, S. G. *Virology* 67(2):344-355; 1975.

To determine if human cells are unique and able to control expression of certain murine sarcoma virus (MSV) functions, second-generation MSV from the S+L- human cells is recloned in dog, mink, and back into mouse cells (3T3FL). Heterologous host dog and S+L- cell clones, like human S+L- cell clones, failed to release viral-type reverse transcriptase into culture supernatant fractions. All second-generation homologous mouse S+L- cell clones again released viral reverse transcriptase in supernatant fractions, indicating that the MSV genome had not been altered in this function. Using (dT)₁₂₋₁₈-cellulose and phosphocellulose chromatography of cellular polymerase preparations, no intracellular buildup of unreleased murine reverse transcriptase was detected in the S+L- clones. The data sug-

gest that the MSV genome is defective in the information for the viral core protein RNA-dependent DNA polymerase. The implications of these findings for the genetic study of MSV are discussed.

- 6249 LOCATION OF HISTONES ON SIMIAN VIRUS 40 DNA. (Eng.) Polisky, B. (Dept. Biochemistry and Biophysics, Univ. California, San Francisco, Calif. 94143); McCarthy, B. *Proc. Natl. Acad. Sci. USA* 72(8):2895-2899; 1975.

The physical location of histone molecules in a simian virus 40 (SV40) DNA-histone complex isolated from purified virions was examined using site-specific restriction endonucleases. The complex contains four histone species (F2b, F2a1, F2a2, and F3) but lacks histone F1. Histones prevent complete cleavage of SV40 DNA by two restriction enzymes, *Hind* III and *Eco*RI. From the pattern of DNA fragments resulting from cleavage of the histone-DNA complex by the *Hind* III endonuclease, which makes six breaks on purified SV40 DNA, it was concluded that histones are randomly arranged on SV40 DNA relative to restriction enzyme cleavage sites. The *Eco*RI endonuclease, which makes one break in SV40 DNA, was used to determine the degree of physical coverage of the SV40 DNA molecule by histones. Eighty percent of the *Eco*RI sites in the complex are accessible to the enzyme, while 20% are "closed". This degree of coverage is consistent with the mass ratio of DNA:histone in the complex as revealed by the buoyant density of the formaldehyde-fixed complex. It is concluded that the histones in the complex are located randomly on the SV40 genome and cover approximately 20% of the DNA. These results suggest that the histone species F2b, F2a1, F2a2, and F3 are bound without regard to the nucleotide.

- 6250 APPEARANCE OF SMALLER MANNOSYL-GLYCOPEPTIDES ON THE SURFACE OF A HUMAN CELL TRANSFORMED BY SIMIAN VIRUS 40. (Eng.) Ceccarini, C. (Dept. of Biological Sciences, Hunter Coll., CUNY, New York, N.Y. 10021). *Proc. Natl. Acad. Sci. USA* 72(7):2687-2690; 1975.

The size distribution of surface glycopeptides from growing normal human fibroblast cells (WI 38) was compared with that of nongrowing normal cells and also with the surface glycopeptides from simian virus 40 (SV40)-transformed cells. Cell surface material from growing WI 39 cells (labeled with [³H]fucose) was mixed with that from nongrowing cells (labeled with [¹⁴C]-fucose) and, after extensive digestion with Pronase, the glycopeptides were chromatographed on a Sephadex G-50 column. The fucosyl surface peptides from growing cells were enriched in high-molecular weight species, compared with those from nongrowing cells. However, the fucosyl surface glycopeptides derived from SV40-transformed WI 18Va cells (labeled with [¹⁴C]-fucose) appeared to have a size distribution similar to those from rapidly growing normal cells. Thus, the enrichment in high-molecular weight species in these cells might be growth-dependent rather than transformation-dependent. When radioactive mannose (³H and ¹⁴C) was used, rapidly growing and nongrowing WI 38 cells behaved in the expected manner: the mannosyl glycopeptides from the growing

cells had a broader profile than those of nongrowing cells. However, the mannosyl glycopeptides from the surface of the SV40-transformed cells were strikingly smaller than those from rapidly growing normal cells. Therefore, differences in size distribution may not be adequate criteria for evaluating the growth-dependent alterations in cell surface glycopeptides.

- 6251 ALTERATIONS IN SVT2 CELL TRANSFER RNAs IN RESPONSE TO CELL DENSITY AND SERUM TYPE. (Eng.) Katze, J. R. (Univ. Southern California Sch. Med., Los Angeles). *Biochim. Biophys. Acta* 383(2):131-139; 1975.

The chromatographic elution profiles of transfer RNA^{Asn} (tRNA^{Asn}), tRNA^{Asp}, tRNA^{His}, and tRNA^{Tyr} from Simian virus 40 (SV40)-transformed cells grown in fetal calf serum or calf serum-supplemented media were examined. A BALB/3T3 (clone A31) mouse cell line and an SV40-transformed subclone (SVT2) were the cells involved and a reversed-phase chromatograph with an RPC-5 column was used. Despite wide variances in individual peak sizes, a study of the effect of cell density and fetal calf serum *vs* calf serum on tRNA^{Asp} isoaccepting species revealed a much higher concentration of tRNA^{Asp} in early peaks at all cell densities of fetal calf serum-grown cells relative to calf serum-grown cells. In addition to tRNA^{Asp}, fetal calf serum growth induced a marked relative increase in tRNA^{Asn}, tRNA^{His}, and tRNA^{Tyr}; a more detailed comparison indicated that the distribution of isoaccepting tRNA^{Tyr} is also influenced by cell density. Additional high- *vs* low density comparisons indicated that only tRNA^{Lys} and tRNA^{Phe} exhibit prominent differences. The changes effected by BrCN treatment of tRNA^{Asp}, tRNA^{Asn}, tRNA^{His}, and tRNA^{Tyr} give evidence of the influence of fetal calf serum-growth on the formation of a structurally uncharacterized minor nucleotide, Q. A comparison of the chromatographic profiles of tRNA^{Asp} from a variety of mammalian sources suggested a rough correlation between cell growth characteristics and the isoaccepting pattern. It is suggested that the elution profile alterations affect the extent of modifications of a specific G residue to the minor nucleoside Q, that this process differs between untransformed and transformed cells, and that cell density and other density-dependent tRNA modifications influence the Q content.

- 6252 SV40 INDUCED POLYPEPTIDES IN INFECTED AND TRANSFORMED CELLS. (Eng.) Ho, L. (Dept. Bacteriology, Univ. Coll. Hosp. Medical Sch., London WC 1 E 6JJ, England); Cohen*, A. *Arch. Virol.* 48(4):327-333; 1975.

Qualitative and quantitative differences in the synthesis of virus-induced polypeptides in simian virus 40 (SV40)-infected permissive and nonpermissive, and transformed cells are reported. Cell lines used in the investigation were CV-1 (permissive), 3T3 (nonpermissive), and T22 (an intermediate line). Virus-induced polypeptides in SV40-infected (100 PFU/cell) cell homogenates, pulse labeled with [¹⁴C]-protein hydrolysate (2.5 µCi/ml) at different times in the virus growth cycle, were identified in

polyacrylamide gels by coelectrophoresis with structural polypeptides of purified virions and uninfected cell homogenates. In CV-1, the structural polypeptide VP1 was first detected at 17 hr, immediately after the onset of viral DNA synthesis, increased rapidly to a peak at 24 hr and continued throughout the infective cycle. The second structural polypeptide, VP2, showed the same overall pattern of synthesis but did not appear until 31 hr after infection. The internal structural polypeptide components, VP3-5, were synthesized between 24-32 hr only, at rates which increased and decreased rapidly. None of these polypeptides could be detected in the presence of cytosine arabinoside (15 µg/ml) which reduced viral DNA synthesis by 99% and are therefore identified as late polypeptides. Three polypeptides were identified in infected cells which were not present in the SV40 virions or uninfected cells and were designated nonstructural viral polypeptides (NSVP). NSVP 1 and 2 were synthesized in the presence of cytosine arabinoside (15 µg/ml) and are therefore early functions. NSVP 3 was inhibited by cytosine arabinoside and is identified as a late function. Electrophoresis of whole cell or nuclear homogenates from permissive CV-1 and nonpermissive 3T3 cells and their counterparts transformed by SV40 did not reveal any differences between normal and transformed cells. Electrophoresis of soluble nuclear extracts precipitated with 20% ammonium sulfate, revealed a polypeptide peak of 69K molecular wt in both T-22 and SV/3T3 cells which was absent in their untransformed parents. It is suggested that this peak is T-antigen. The results suggest that full expression of the early functions of SV40 are not required for cell transformation. The two kinetic patterns of virus-induced polypeptide synthesis suggest that in both the early and late phases of infection at least two classes of messenger RNA code for virus-induced products. It is concluded that the qualitative and quantitative differences in synthesis of virus-induced polypeptides reflect the control of virus genetic expression for which the existence of discrete species of messenger RNA would provide a possible mechanism.

- 6253 PHOSPHOPROTEINS: STRUCTURAL COMPONENTS OF ONCORNAVIRUSES. (Eng.) Pal, B. K. (Univ. South. California Sch. Med., Los Angeles); Roy-Burman, P. *J. Virol.* 15(3):540-549; 1975.

Specific phosphoproteins in murine and feline type C oncornaviruses were examined as structural components of these virions. Purified wild mouse virus 275 (derived from CNS tissue of a paralyzed Swiss mouse that had been inoculated with wild mouse 1504E virus originating from a wild mouse embryo cell culture) was labeled with ^3H -labeled amino acids and [^{32}P]phosphate. The preparation was dissociated by treatment with guanidine hydrochloride, separated into six major components by guanidine-agarose chromatography, and two of the peaks were found to contain superimposed ^3H and ^{32}P radioactivities. Treatment with RNase prior to chromatography suggested that the polypeptide p12 (one of the peaks) might be a phosphoprotein. Similar analysis of the Rauscher strain of murine leukemia virus (MuLV-R), of the Kirsten strain

of murine sarcoma virus (Ki-MSV), of the original mouse erythroblastosis virus (MEV), and of the wild mouse type C virus 292 (WM-292) showed that the p12 of each virus was associated with both ^3H and ^{32}P radioactivities. RNase-treated Gardner-Arnstein strain of feline leukemia virus (FeLV-GA) also contained both ^3H and ^{32}P labels in a single major polypeptide (p12: about 12,000 molecular weight). Ki-MSV contained a second major phosphoprotein of about 10,000 molecular weight. MEV also contained a second major phosphoprotein either identical to or comigrating with the virion glycoprotein of about 74,000 molecular weight. The major phosphoprotein of RD-114 virus (an endogenous feline type C virus) was about 16,000 molecular weight. The major phosphoamino acid of the p12 polypeptide of MEV was identified as phosphoserine, and that of the p16 polypeptide of RD-114 virus was phosphothreonine. These phosphoproteins are structural components of these virions.

- 6254 HUMAN SERUM Lyses RNA TUMOUR VIRUSES. (Eng.) Welsh, R. M., Jr. (Dept. Immunopathology and Molecular Immunology, Scripps Clinic and Res. Foundation, La Jolla, Calif. 92037); Cooper, N. R.; Jensen, F. C.; Oldstone, M. B. A. *Nature* 257(5527):612-614; 1975.

Human sera from 5 cord blood samples, 6 leukemic patients, and 21 healthy adults was tested for the ability to lyse RNA tumor viruses. An XC cell plaque reduction assay revealed that a 1:2 dilution of human serum inactivated 2.5×10^5 plaque-forming units of Moloney leukemia virus (MLV). Heated serum (56 C, 30 min) did not lyse viruses, nor would serum from animals tested (guinea pigs, rabbits, BALB/c mice, and NIH Swiss mice). To determine the mechanisms of viral inactivation, SCRF 179 cells were grown in medium containing ^3H -uridine ($15 \mu\text{Ci ml}^{-1}$, 40-50 Ci mM^{-1}). Labeled MLV was incubated for 30 min at 37 C with bovine serum albumin (BSA), heated human serum or fresh human serum, and analyzed by sucrose gradient ultracentrifugation. After being incubated with either BSA or heated human serum the virus-associated radioactive counts sedimented to the lower portion of the gradient. When MLV was mixed with fresh human serum, most of the label remained at the top portion of the gradient, demonstrating that fresh human serum released RNA from the virus. Fresh, but not heated, human serum released RNA-dependent DNA polymerase (RDDP) from six different viruses (avian myeloblastosis virus, feline leukemia virus, Moloney leukemia virus, Rauscher leukemia virus, simian sarcoma virus, and wild mouse virus 1504). Human sera deficient in functional complement (C) failed to release RDDP, suggesting that C was required for viral lysis. The possibility that lysis of oncornaviruses occurred because of C activation by components of fetal calf serum retained on the viral surface was ruled out by further experimentation. No evidence for antibody involvement could be found, however, it was possible that trace amounts of heat labile antibody were present. The role, if any, of other serum factors is not known. It is suggested that if oncornaviruses do infect man, lysis of these viruses may represent a natural resistance mechanism which would limit the transmission and expression of oncornavirus.

- 6255 DETECTION OF ONCORNAVIRUSES BY USE OF MOLECULAR HYBRIDIZATION BETWEEN NUCLEIC ACIDS. (Fre.) Larsen, C. J. (Laboratoire d'Hématologie expérimentale, Hôpital Saint-Louis, 2, place du Docteur Alfred-Fournier, 75475 Paris, Cedex 10., France); Marty, M. *Bull. Cancer (Paris)* 62(2):195-204; 1975.

Experimental work on the use of RNA-dependent DNA polymerase (reverse transcriptase) in detecting synthesis of viral nucleotide sequences in DNA or RNA of virus-producing or nonproducing host cells is reviewed. Two methods for utilizing reverse transcriptase are described: the exogenous method using purified enzyme and an exogenous host cell such as hemoglobin and the endogenous method using the purified, active virus to stimulate the synthesis of complementary-DNA (c-DNA) in a host cell. Techniques requiring hybridization between c-DNA and cellular DNA and RNA have been developed to detect the presence of the viral nucleotide sequences in the host cell. In order to prove the viral-induced c-DNA did not exist prior to infection with virus or addition of reverse transcriptase, cells without endogenous virus must be used or host viral DNA sequences eliminated by hybridization with normal cellular DNA. Hybridization with c-DNA has permitted isolation of specific viral RNA. It has been established that cell lines with endogenous virus produce more than twice as much viral RNA as transformed, virus-infected cells. This poses the question whether complete transcription of the viral genome takes place in an exogenously infected cell. Location of viral RNA on free and membrane-bound polyribosomes has been established. Research from 1972-1974 on the presence of nucleotide sequences homologous to oncornaviral genomes in human tumor cells is tabulated. The question remains whether viral elements in the tumor cells induce the neoplastic process or simply co-exist with it.

- 6256 TRANSFORMATION OF CULTURED HUMAN EMBRYONIC FIBROBLASTS BY ONCORNAVIRUS-LIKE PARTICLES RELEASED FROM A HUMAN CARCINOMA CELL LINE. (Eng.) Balabanova, H. (Hadassah Hosp., Jerusalem, Israel); Kotler, M.; Becker, Y. *Proc. Natl. Acad. Sci. USA* 72(7):2794-2798; 1975.

The spontaneous release of virus-like particles from cultured (human adenocarcinoma) tumor cells and the transforming ability of these particles is reported. A fibroblast-like cell culture was established from a stomach biopsy of a patient with metastatic adenocarcinoma. One of the cultures, at the sixth passage level, left unattended for a month at 37 C, produced density of 1.22-1.26 g/ml, 70 S RNA and RNA-instructed an epithelioid cell line, designated HCCL (human carcinoma cell line), was established. The HCCL cells released particles possessing the characteristics of oncornaviruses: density 1.175 g/ml, cores with a density of 1.22-1.26 g/ml, 70.S RNA and RNA-instructed DNA polymerase activity (deoxynucleosidetriphosphate: DNA deoxynucleotidyltransferase). This DNA polymerase synthesized DNA x 60-70S RNA hybrids which

were not detected in the presence of ribonuclease. Inoculation of particles released from HCCL cells into cultures of human embryo muscle fibroblasts resulted in the appearance of foci of transformed cells. Similar inoculation of human embryonic kidney and skin culture did not result in transformation. The particles from the transformed human cells also resembled type-c oncornaviruses.

- 6257 DISTRIBUTION OF THREE CLASSES OF ENDOGENOUS TYPE-C RNA VIRUSES AMONG INBRED STRAINS OF MICE. (Eng.) Stephenson, J. R. (Natl. Cancer Inst., Bethesda, Md. 20014); Reynolds, R. K.; Tronic, S. R.; Aaronson, S. A. *Virology* 67(2):404-414; 1975.

The distribution of three prototype endogenous type-C RNA viruses, N-tropic BALB:virus-1, xenotropic BALB:virus-2, and a xenotropic virus isolated from NIH Swiss and NZB mice was studied in a number of inbred mouse strains (C57BL/6N, NIH Swiss/N, BALB/cN, CBA/N, A/HeN, DBA/2N, NZB/N, NZW/N, C3H/HeN, AKR/N, C58/J, C57BL/10Sn, and SWR/J) of widely diverse geographic origin. The cell lines were established from individual embryos of each of the strains and were exposed to 20 µg/ml iododeoxyuridine for 18 to 20 hr. Following treatment, the cells were cocultivated with human A673 and NIH/3T3 assay cells. The cultures were assayed for virion-associated reverse transcriptase activity at biweekly intervals. Purified virion p12 polypeptides of different endogenous type-C viruses were defined by type-specific immunoassays using p12 antigens of BALB:virus-2 and an NIH Swiss type-C virus as prototype viruses for two immunologically distinguishable classes of xenotropic virus. Antiserum prepared against the respective detergent-disrupted virus was used to precipitate the corresponding ¹²⁵I-labelled p12 polypeptide in a homologous type-specific assay for each virus. Three of the strains tested for chemical induction of virus, C58, AKR, and NZW, spontaneously released a virus that propagated at high titer in NIH Swiss cells but was not infectious for A673 cells. Cells of a majority of the strains tested were activated by iododeoxyuridine to release a virus that grew to high titer in NIH/3T3 and A673 cells. One strain, NZB, spontaneously released a xenotropic virus that grew in A673 cells. There was no detectable N-tropic virus-release from the same cells even after iododeoxyuridine activation. Embryo cell lines of two strains, NIH Swiss and SWR, showed no evidence of either N-tropic or xenotropic virus-release spontaneously or following chemical exposure. The endogenous xenotropic virus isolated from NIH Swiss and NZB mice was invariably detected in strains of wide geographic origin, while the other two viruses exhibited a more limited distribution. The authors suggest that the NIH Swiss xenotropic virus has been present within the mouse genome for the longest period of time and that the other two endogenous type-C RNA viruses may have arisen from this virus. The differences in biologic regulation of each virus may be due to the evolution of specific controls subsequent to the origin of each viral locus.

- 6258 BIOLOGICAL PROPERTIES OF A TYPE C VIRUS ISOLATED FROM A HUMAN X MOUSE HYBRID CELL LINE. (Eng.) Gazdar, A. F. (Natl. Cancer Inst., Bethesda, Md. 20014); Russell, E. K.; Minna, J. *Proc. Soc. Exp. Biol. Med.* 149(3):688-692; 1975.

The biological properties of HMV-1 virus (a type C virus), spontaneously released from a human VA2 x C57BL/6 mouse hybrid cell line, were determined and compared with those of radiation leukemia virus (RadLV), the prototype B-tropic mouse virus isolated from C57BL/6 mice. The plaque-forming abilities of the HMV-1 and RadLV were compared. C57BL/6 embryo cells were infected with both viruses, and at several time points after infection, clarified supernatant fluids were tested for RNA-dependent DNA polymerase activity and ability to form plaques by the Al-2 (a clone of sarcoma virus positive, helper virus negative-transformed BP cells) direct assay and XC indirect assay. Virus-neutralization tests were performed using a plaque-reduction assay. The host range of the HMV-1 virus varied with the cellular passage level. Initially the virus readily infected B-type cells and the wild mouse cell line SC-1. After several further cell passages, virus replication could only be detected in SC-1 cells. RadLV also had a similar host range. The virus stocks used for infection in the virus assays had considerable RNA-dependent DNA polymerase activity but little or no plaque-forming abilities. The plaque-forming abilities of both viruses, however, gradually increased after passage in new host cells. Both viruses were neutralized by AKR antisera but not by FMR antisera. Newborn C57BL/6 mice injected ip with concentrates of SC-1 passaged HMV-1 virus remained healthy and tumor-free over a 1-yr period. The HMV-1 virus was capable of rescuing the defective murine sarcoma virus genome from Al-2 cells. *In vitro* focus formation by the murine sarcoma virus pseudotype so obtained was two-hit, and was nononcogenic in mice. Addition of optimal amounts of helper virus resulted in one-hit focus formation as well as oncogenicity. The authors conclude that HMV-1 virus is nononcogenic, and is either RadLV or a biologically similar virus.

- 6259 GROWTH AND DIFFERENTIATION IN CULTURE OF LEUKEMIC LEUKOCYTES FROM A PATIENT WITH ACUTE MYELOGENOUS LEUKEMIA AND RE-IDENTIFICATION OF TYPE-C VIRUS. (Eng.) Gallagher, R. E. (Natl. Cancer Inst., Bethesda, Md. 20014); Salahuddin, S. Z.; Hall, W. T.; McCredie, K. B.; Gallo, R. C. *Proc. Natl. Acad. Sci. USA* 72(10):4137-4141; 1975.

Conditioned medium from a culture of whole human embryo cells (WHE-1) stimulated prolonged exponential growth in suspension culture of WBC from a patient with acute myelogenous leukemia (AML). The conditioned medium was prepared by growing diploid WHE-1 cells to confluency in antibiotic-free McCoy's 5A medium containing 10% fetal calf serum. WBC (1.25×10^6) from the AML patient (a 61-yr-old woman) were seeded in RPMI 1640 media containing heat-inactivated 20% fetal calf serum and 50 µg/ml gentamicin (which was discontinued after two passages), either on a sub-confluent monolayer of viable WHE-1 cells or with 10% WHE-1 cell conditioned filtered medium. Ten to 20% of the cultured cells consistently differenti-

ated into mature granulocytes including neutrophils, eosinophils, and basophils. The proportion of lymphocytes declined after culturing, and tests for Epstein-Barr virus antigens were negative. An abnormality of a G group chromosome was observed in some metaphases from the patient's fresh bone marrow and from the cultured WBC, indicating growth *in vitro* of leukemic cells. After 4-10 wk in culture, a budding type-C virus was continuously released by the cultured WBC, predominantly by undifferentiated blast cells. This virus was originally identified in three different cultures of a peripheral blood specimen obtained at the time of diagnosis. Subsequently, this virus was identified by reverse transcriptase (RNA-dependent DNA polymerase) assays and by electron microscopy in cultured WBC from a bone marrow specimen obtained 14 mo later from the same patient. Virus produced by cultures of both specimens is closely related, if not identical, to the woolly monkey type-C virus.

- 6260 INFECTIOUS PRIMATE TYPE C VIRUSES: THREE ISOLATES BELONGING TO A NEW SUBGROUP FROM THE BRAINS OF NORMAL GIBBONS. (Eng.) Todaro, G. J. (Natl. Cancer Inst., Bethesda, Md. 20014); Lieber, M. M.; Benveniste, R. E.; Sherr, C. J.; Gibbs, C. J., Jr.; Gajdusek, D. C. *Virology* 67(2):335-343; 1975.

Three type C viruses (GBr-1, GBr-2, and GBr-3) were isolated by cocultivation of normal gibbon brain tissues with cultured mammalian cell lines. The tissues, all frozen since 1968, were obtained from two animals inoculated with brain extracts from human patients with kuru and from one uninoculated cagemate. By viral interference tests and by immunologic studies of the viral polymerases and major internal structural proteins (p30), the new isolates were found to be typical members of a group of mammalian type C viruses infectious for primates. By nucleic acid hybridization, the viruses isolated from the gibbon brains, while highly related to one another, could be readily distinguished from the previously isolated type C viruses of this group. Based on these hybridization techniques, the infectious primate type C viruses isolated to date can be classified into four distinct subgroups (Woolly monkey-SSV/SSAV; Gibbon type 1-GALV-1; Gibbon type 2-GALV-SEATO; and Gibbon type 3-GBr-1, GBr-2, GBr-3).

- 6261 ISOLATION OF AN ENDOGENOUS C-TYPE RNA VIRUS FROM *MUS MUSCULUS MOLOSSINUS*. (Eng.) Bedigian, H. G. (Jackson Lab., Bar Harbor, Maine 04609); Meier, H. *J. Natl. Cancer Inst.* 55(4):1007-1010; 1975.

A type-C RNA virus was isolated from spleen and kidney tissue of the Japanese field mouse, *Mus musculus molossinus*, with or without cocultivation of the tissues with normal rat kidney cells transformed by the Harvey sarcoma virus (H-NRK cells). Supernatants from mouse cells cocultivated with H-NRK cells produced a pseudotype sarcoma virus that could transform rhabdomyosarcoma (RD), rabbit cornea (SIRC), and NRK cells 19 days after infection. The super-

nant could not transform feline embryo cells, SWR/J or BALB/cJ mouse embryo cells, or BALB/c 3T3 cells. In the absence of cocultivation, virus activity was detected in RD, SIRC, and NRK cells 28 days after infection with supernatants from *M. musculus molossinus* spleen and kidney cultures. The virus banded at a density of 1.16 g/ml in a continuous sucrose density gradient and contained an RNA-dependent DNA polymerase. Electron microscopy showed budding and free virus particles in virus-positive RD cultures. Since the virus isolated cannot infect and replicate within cells of its own species or a distantly related species (*Mus musculus musculus*), genetic transmission of the virus is necessary. *M. musculus molossinus* cells therefore contain an endogenous xenotropic type-C virus with properties similar to other xenotropic viruses. These findings in feral mice, along with previous demonstrations of C-type RNA virus release from virus-free mouse embryo cells, support the presence of genetic determinants of murine leukemia virus in all members of the genus *Mus*.

6262 EXPRESSION AND DETECTION OF ENDOGENOUS MOUSE C-TYPE RNA VIRUSES. (Eng.) Lowy, D. R. (Building 7, Room 304, Natl. Inst. Allergy and Infectious Diseases, Bethesda, Md. 20014); Teich, N. M.; Chattopadhyay*, S. K. *In Vitro* 10(5/6):253-259; 1974.

Recent data relating to endogenous, nontransforming mouse C-type viruses is reported. Many naturally occurring C-type RNA viruses are of endogenous origin. The genetic information for synthesizing these RNA viruses is present in the DNA of normal mouse cells, probably as part of their chromosomal DNA. Some C-type viruses infect mouse cells, (homotropic virus), while others infect certain tissue culture cells from other species but not mouse fibroblasts (xenotropic virus). All mouse strains studied appear to contain endogenous xenotropic viral genomes. However, based on the regularity with which homotropic virus is detected, inbred mice can be divided into high, low, and nonvirus-yielding strains. Nucleic acid hybridization studies have shown that DNA from high virus strains contains fewer copies, and DNA from nonvirus strains lacks a significant portion of the homotropic virus genome. *In vivo* and *in vitro* genetic studies support the nucleic acid hybridization results. In addition, high virus mouse strains are more likely than low virus strains to release virus that will replicate efficiently in their own cells. Techniques for the detection and activation of C-type viruses have permitted the recent studies of endogenous viruses. Sensitive virus assay techniques include a quantitative virus plaque assay for homotropic virus, measurement of the murine group specific antigen, use of reverse transcriptase as a virus-specific marker, and "rescue" of defective sarcoma virus from transformed nonproducer cells. The first efficient activators of the C-type viruses were the halogenated thymidine analogues 5-iododeoxyuridine and 5-bromodeoxyuridine, which activate xenotropic as well as homotropic viruses. Protein inhibitors are also efficient virus inducers in some systems, and they appear to induce xenotropic virus selectively. Im-

munologically mediated virus activation can be used to induce homotropic virus in some instances and xenotropic virus in others.

6263 STUDY OF THE METABOLIC ACTIVITY OF A CONTINUOUS LINE OF HUMAN EMBRYO LUNG CELLS INFECTED WITH ONCORNAVIRUS TYPE D. (Rus.) Nosik, N. N. (D. I. Ivanovski Inst. Virology, Acad. Medical Sciences, Moscow, USSR); Ershov, F. I. *Vopr. Virosoł.* (4):442-445; 1975.

The intensity of DNA, RNA and protein syntheses in the cells of a continuous culture line of human embryo lung cells (HEL) before and after infection with an oncornavirus isolated from human Hep-2 cell cultures was investigated. The metabolic activity of HEL cells was studied in two culture groups infected with the oncornavirus; one group was grown in the presence of a carcinogenic agent after the infection. Noninfected HEL cells with and without the carcinogenic agent served as controls. Scintillographic determination of a radioactive labeling substance in the cell culture was very sensitive. HEL cells of the second passage were used to determine metabolic activity. The results showed a considerable stimulation of RNA syntheses. DNA and protein synthesis in the infected cell cultures reached 2-3 times the level of controls. Increased radioactive label incorporation into the infected cells coincided with a tripled RNA synthesis. The protein formation in the noninfected cell cultures with and without carcinogenic agent did not vary from each other and was two times lower than in the infected cell cultures. Raised levels of DNA, RNA and protein synthesis in the infected cultures suggest a cytoproliferative effect of the oncornavirus.

6264 THYMUS DEPENDENCE OF VIRAL ANTIGENS. (Eng.) Burns, W. H. (Natl. Inst. Dental Health, Bethesda, Md. 20014); Billups, L. C.; Notkins, A. L. *Nature* 256(5519):654-656; 1975.

The humoral antibody responses of athymic nude (*nu/nu*) mice after infection with 12 viruses from nine major virus groups were compared with those of normal littermates (*nu/+* or *+/+*). The viruses used were Cocksackie B1, encephalomyocarditis (EMC) virus, influenza PR8, simian virus 5, Sendai virus, vesicular stomatitis virus (VSV), Sindbis virus, minute virus of mouse, mouse adenovirus, Herpes simplex type I, and simian virus 40. The nude mice and their normal littermates were infected ip; their sera were then assayed for neutralizing, hemagglutination-inhibiting, and complement-fixing antibodies to certain antigens. Sustained antibody responses to all 12 viruses were markedly thymus-dependent. Nude mice, however, made early transient responses equal in magnitude to those of normal litters to the picornaviruses (Cocksackie B1 and EMC virus), to VSV, and to Sindbis virus. Antibody production in nude mice to the Sindbis antigen(s) that react with neutralizing antibody was sustained for two weeks, and was solely immunoglobulin M (IgM); the latter was indicated by its appearance in the IgM fraction after column chromatography of serum on Sephadex G-200 and by its sensitivity to 2-mercaptoethanol. Normal

littermates produced IgG as well as IgM antibody to this antigen; these mice, unlike nude mice, produced large secondary responses of predominantly IgG antibody. The Sindbis antigen(s) concerned are found on two virion membrane glycoproteins. The switch from IgM to IgG synthesis and the elicitation of secondary IgG responses to protein antigens is highly thymus-dependent. Depletion of T cells may result in deficient antibody production as well as a diminution of effector cells involved in cell-mediated immunity.

6265 GENETIC ANALYSIS OF ADENOVIRUS TYPE 2.
I. ISOLATION AND GENETIC CHARACTERIZATION OF TEMPERATURE-SENSITIVE MUTANTS. (Eng.) Bégin, M. (Centre Hospitalier Universitaire, Sherbrooke, Quebec, Canada); Weber, J. *J. Virol.* 15(1):1-7; 1975.

6266 GENETIC CONTROL AND ONCOGENICITY OF ENDOGENOUS AND EXOGENOUS AVIAN RNA TUMOR VIRUSES. (Eng.) Weiss, R. A. (Imperial Cancer Res. Fund Lab., London, England); Crittenden, L. B.; Purchase, H. G.; Vogt, P. K. *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 248-253.

6267 GENETIC TRANSMISSION IN MICE OF ENDOGENOUS LEUKEMIA VIRUS (MuLV), SPONTANEOUS LEUKEMIA AND SUSCEPTIBILITY TO LEUKEMIA INDUCTION BY 3-METHYLCHOLANTHRENE (MCA) [abstract]. (Eng.) Duran-Reynals, M. L. (Albert Einstein Coll. Med., Bronx, N.Y.); Lilly, F. *Proc. Am. Assoc. Cancer Res.* 16:76; 1975.

6268 HETEROGENEITY OF ENDOGENOUS MURINE C-TYPE VIRUS GENE EXPRESSION. (Eng.) Pincus, T. (Memorial Sloan-Kettering Cancer Center, New York, N.Y.); O'Donnell, P. V.; Tung, J.-S.; Fleissner, E. *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 260-267.

6269 INHIBITION OF RNA DEPENDENT DNA POLYMERASE OF ONCORNAVIRUSES BY 5-TUNGSTO-2-ANTIMONIATE [abstract]. (Eng.) Sinoussi, F. (Institut Pasteur, 94015-Paris, France). *Proc. Am. Assoc. Cancer Res.* 16:201; 1975.

6270 STUDY OF THE MOUSE ONCORNA VIRUS GROUP-SPECIFIC ANTIGEN SYNTHESIS IN CHRONICALLY INFECTED CELLS. (Rus.) Al'tshtein, A. D. (D. I. Ivanovskii Inst. Virology, Acad. Med. Sci. U.S.S.R., Moscow, USSR); Argirova, R. M.; Gerasina, S. F.; Karelin, V. P.; Zhdanov, V. M. *Vopr. Virusol.* (1): 94-96; 1975.

6271 APPEARANCE OF C-TYPE VIRUS PARTICLES AFTER CO-CULTIVATION OF HUMAN LUNG TUMOR AND RAT (XC) CELLS [abstract]. (Eng.) Gabelman, N. (Mt.

Sinai Sch. Med., New York, N.Y.); Waxman, S.; Smith, W.; Douglas, S. D. *Proc. Am. Assoc. Cancer Res.* 16:33; 1975.

6272 ULTRASTRUCTURAL STUDIES OF HUMAN PROSTATIC NEOPLASIA [abstract]. (Eng.) Ohtsuki, Y. (M. D. Anderson Hosp. and Tumor Inst., Houston, Tex.); Seman, G.; Maruyama, K.; Bowen, J. M.; Dmochowski, L.; Johnson, D. E. *Proc. Am. Assoc. Cancer Res.* 16:59; 1975.

6273 THE NEUTRALIZATION OF 334C MURINE LEUKEMIA VIRUS INFECTIVITY IN AN XC ASSAY BY SERUM BUT NOT MILK FROM 334C VIRUS-IMMUNIZED FEMALES [abstract]. (Eng.) Tidwell, T. (Roswell Park Mem. Inst., Buffalo, N.Y.). *Proc. Am. Assoc. Cancer Res.* 16:130; 1975.

6274 BIOCHEMICAL CHARACTERIZATION OF Fv-1 ALLELE CELL EXTRACTS INHIBITING MOUSE LEUKEMIA VIRUS INFECTION [abstract]. (Eng.) Yang, W.-K. (Oak Ridge Natl. Lab., Tenn.); Tennant, R. W.; Schluter, B.; Myer, F.; Brown, A. *Proc. Am. Assoc. Cancer Res.* 16:138; 1975.

6275 ACTIVATION OF MURINE LEUKEMIA VIRUS BY GAMMA IRRADIATION [abstract]. (Eng.) Otten, J. A. (Biol. Div., Oak Ridge Natl. Lab., Tenn.); Quarles, J. M.; Tennant, R. W. *Proc. Am. Assoc. Cancer Res.* 16:72; 1975.

6276 PASSAGE OF ROUS SARCOMA VIRUS THROUGH THE CELL OF QUAIL [abstract]. (Jpn.) Toyoshima, K. (Inst. Microorganism, Osaka Univ., Osaka, Japan); Nomaguchi, H.; Tani, S.; Yoshida, M. *Virus (Tokyo)* 24(3):280-281; 1975.

6277 ALPHA-ALPHA TYPE CONVERSION OF BETA-TYPE ROUS SARCOMA VIRUS *IN VIVO* [abstract]. (Jpn.) Igarashi, H. (Sch. Bacteriology, Nagasaki Univ., Nagasaki, Japan); Shitamori, T.; Miyamoto, B. *Virus (Tokyo)* 24(3):280; 1975.

6278 A TENTATIVE PHYSICAL MAP OF THE GENOME OF AN AVIAN TUMOR VIRUS [abstract]. (Eng.) Coffin, J. M. (Inst. Molekularbiologie I, Univ. Zurich, CH-8049 Zurich, Switzerland); Billeter, M. A. *Experientia* 31(6):736; 1975.

6279 DNA FORM OF THE GENOME OF ONCORNAVIRUSES. (Fre.) Hill, M. (Institut de Cancerologie et d'Immunogenetique, 14, avenue P. Vaillant-Couturier, F94800 Villejuif, France); Hillova, J.; Goubin, G.; Mariage, R.; Dantchev, D. *Bull. Cancer (Paris)* 62(2):183-194; 1975.

6280 SYSTEMIC BCG INFECTION IN MARMOSETS [abstract]. (Eng.) Schauf, V. (Univ. Ill., Chicago); Landau, W.; Falk, L. *Proc. Am. Assoc. Cancer Res.* 16:102; 1975.

6281 CELL-SURFACE ANTIGENS ON THE RAT TUMORS
INDUCED BY FRIEND LYMPHATIC LEUKEMIA VIRUS
[abstract]. (Jpn.) Kuzumaki, N. (Cancer Inst.,
Hokkaido Univ., Sch. Med., Sapporo, Japan); Kobayashi,
H. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual
Meeting, October 1975.* p. 54.

6282 SPECIES DIFFERENCES IN THE DEVELOPMENTAL
MANNER OF INTRACRANIAL LESIONS INDUCED BY
MOLONEY MURINE SARCOMA VIRUS [abstract]. (Jpn.)
Ogawa, K. (Okayama Univ. Medical Sch., Okayama,
Japan); Motoi, M.; Jinno, K.; Nakamura, S.; Ikubo,
T.; Ohmori, M.; Tsutsumi, A. *Gann, Proc. Jpn.
Cancer Assoc., 34th Annual Meeting, October 1975.*
p. 28.

6283 THE EXPERIMENTAL TERATOMAS IN THE RAT
[abstract]. (Jpn.) Sakashita, S.
(Hokkaido Univ. Sch. Medicine, Sapporo, Japan);
Hirai, H. *Gann, Proc. Jpn. Cancer Assoc., 34th
Annual Meeting, October 1975.* p. 28.

See also:

- * (Rev): 6019, 6020, 6021, 6022, 6045, 6050,
6051, 6052, 6053, 6057
- * (Chem): 6172, 6183
- * (Immun): 6290, 6302, 6315, 6321, 6326, 6330,
6334, 6347, 6350, 6354, 6357, 6368,
6369, 6371, 6373, 6378
- * (Path): 6467, 6477, 6481
- * (Epid-Biom): 6499

- 6284 STUDIES CONCERNING THE REGIONAL LYMPH NODE IN CANCER: VIII. EFFECT OF TWO ASYNCHRONOUS TUMOR FOCI ON LYMPH NODE CELL CYTOTOXICITY. (Eng.) Fisher, B. (Univ. Pittsburgh Sch. Medicine, 3550 Terrace St., Pittsburgh, Pa. 15261); Wolmark, N.; Coyle, J.; Saffer, E.; Fisher, E. R. *Cancer* 36(2):521-527; 1975.

To provide insight regarding the effect of metastases on host immune responses, tests were made of the cytotoxic capacities of cells from regional lymph nodes (RLNs) and nonregional lymph nodes (NRLNs) of mice carrying asynchronous tumor foci. A spontaneous mammary carcinoma (C3H) or a methylcholanthrene-induced sarcoma (MC) was transferred in female C3HeB/FeJ mice by implanting 1-2 mm fragments sc into the left hind leg distal to the popliteal lymph node. A second tumor was transferred in the same manner to the right foreleg distal to the epitrochlear node. Popliteal and inguinal nodes of tumor-bearing legs were designated as RLNs, and nodes from the right foreleg and axilla were designated as NRLNs. *In vitro* cytotoxicity tests were performed by adding test lymph node cells to monolayers of tumor cells, incubating 48 hr, and scoring the results on a scale of 0 to 5 according to the amount of tumor cell destruction. The results suggested that cytotoxicity by RLN cells (RLNCs) is unique, in that while a primary tumor is present, cells from NRLNs (NRLNCs) possessed less cytotoxicity than RLNCs and failed to increase in response to a second tumor focus in an area drained by the NRLNs. Furthermore, the second tumor focus attenuated cytotoxicity of RLNCs of the primary tumor. Following removal of the primary tumor, RLNCs rapidly lost cytotoxicity and with passage of time were unable to regain that function in response to a second tumor focus. In contrast, NRLNCs demonstrated increased cytotoxicity at any time following removal of the primary tumor when exposed to a second tumor focus. These observations suggested that nodes regional to a distant metastatic focus may be unable to react to it and thus contribute little to the host response generated by the primary tumor. In addition, since RLNs to a primary tumor manifest diminished cytotoxicity in the presence of a distant tumor focus, tumor cells gaining access and lodging in those nodes subsequent to the development of other metastatic foci are likely to proliferate, resulting in the "positive" lymph node. It was proposed that the findings have relevance to the site of administration of specific immunotherapeutic agents and to the significance of the removal of RLNs with a primary tumor.

- 6285 CELL-MEDIATED CYTOTOXICITY TO MOLONEY SARCOMA IN SYNGENEIC AND ALLOGENEIC RATS. (Eng.) Veit, B. C. (Scripps Clin. Res. Found., La Jolla, Calif.); Feldman, J. D. *Int. J. Cancer* 15(3):367-376; 1975.

Cell-mediated cytotoxicity (CMC) in the primary immune response to Moloney sarcoma tumor (MST) in allogeneic and syngeneic rats was studied *in vitro* using a ^{51}Cr -release assay. BN rats were injected with 1×10^7 tumor cells sc and examined during a

20-day postinoculation period for tumor growth, serum cytotoxic antibody, cell-mediated cytotoxicity, and absolute numbers of T-cells per lymphoid organ. Lewis rats were injected with 2×10^7 tumor cells and similarly examined. The CMC in both allogeneic and syngeneic rats was found to be predominantly T-cell-dependent. A minor non-T-cell cytotoxic activity may also have been detected. CMC was presumably directed against tumor and viral related antigens in the syngeneic host and primarily against alloantigens in the allogeneic host. CMC was more vigorous in the allogeneic recipient than in the syngeneic host. This may be due to differences in quantities or immunogenicities of the various antigens involved. Two peaks of T-cells in effector populations were observed during the post-inoculation period. The first peak corresponded to peak T-cell-mediated cytotoxicity on day 8 and the second peak occurred on days 13 or 14 when CMC was minimal or undetectable.

- 6286 ALLOGENEIC TUMOR ENHANCEMENT BY LEVAMISOLE, A NEW IMMUNOSTIMULATORY COMPOUND: STUDIES ON CELL-MEDIATED IMMUNITY AND HUMORAL ANTIBODY RESPONSE. (Eng.) Mantovani, A. (Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157 Milan, Italy); Spreafico, F. *Eur. J. Cancer* 11(8):537-544; 1975.

Modifications in antitumor immune effector mechanisms accompanying enhancing treatment with adjuvant were studied in a system in which facilitation of allogeneic tumor growth occurred after treatment of tumor bearing hosts with levamisole (Leva). Female C3H mice were used and were injected i.p. on day 0 with 5×10^6 or 10^7 cells of the allogeneic L1210 leukemia. In tests involving levamisole, a saline solution of the compound was injected i.p. at a dose of 3 mg/kg from day 1 to day 4. Cells used for cell mediated cytotoxicity (CMC) testing were prepared from spleens of treated and control mice. The CMC test was based on a ^{51}Cr release assay, using an attacker:target cell ratio of 100:1. Sera used for tests of complement-dependent cytotoxicity and for tests of blocking activity were prepared from blood collected from the retro-orbital plexus of the treated and control mice. For tests on effect of levamisole on response to sheep erythrocytes (SRBC), the mice were injected i.p. with 4×10^8 SRBC on day 0 and the number of direct plaque-forming cells (PFC) in the spleens was evaluated on days 4, 5 and 7. The effect of Leva on tumor allograft rejection was that when the allograft consisted of 10^7 cells, 0-20% of the control mice succumbed to progressive tumor growth, while 50-100% of the Leva-treated mice died. Similarly, when the allograft consisted of 5×10^6 cells, none of the control mice succumbed, while about 50% of the Leva-treated mice died of widespread leukemia. The effect of Leva on primary response to SRBC was, at day 7 after antigen stimulation, a doubling of PFC in Leva-treated mice compared to unimmunized mice. These findings, indicating that Leva in the schedule employed was specifically immunosuppressive, was supported by the further findings that treatment of L1210 tumor-bearing mice with Leva brought about a depression of cell-mediated immunity

and serum cytotoxic antibodies and an increased serum blocking activity. It appeared that the low levels of CMC observed in Leva-treated animals played an important role in the enhanced tumor growth.

6287 SUPPRESSION OF SECONDARY CELLULAR IMMUNITY TO A TUMOR ALLOGRAFT BY CYCLOPHOSPHAMIDE AND 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA. (Eng.) Einstein, A. B., Jr. (Univ. Washington Sch. Med., Seattle); Fass, L.; Fefer, A. *Cancer Res.* 35(3): 492-496; 1975.

The effects of cyclophosphamide (CY) and 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) on secondary cellular immune response to allogeneic tumor cells were tested in mice, as reflected by the cytotoxic reactivity of their spleen cells against tumor cells *in vitro* and by the ability of the mice to reject transplanted allogeneic tumor cells *in vivo*. C57BL/6 mice (H-2^b) were immunized with lethally x-irradiated Moloney virus-induced lymphoma cells of BALB/c origin (H-2^d) on days 0 and 10 and received drug on days 11 and 14. Their spleen cells were then tested for reactivity against Moloney virus-induced lymphoma of BALB/c origin by the ⁵¹Cr-release cytotoxicity assay. In non-drug-treated mice the secondary cytotoxic response was maximal on days 14-15, declined rapidly, and recurred after day 21. The cytotoxic effector cells were shown to be 0-bearing T-lymphocytes. CY (180 mg/kg), given on day 11, totally prevented the development of a cytotoxic response and, when given on day 14, abolished the response already established. CY (48 mg/kg) as well as BCNU (33 mg/kg) were almost as suppressive. Immune mice given CY on day 14 and re-immunized on day 36 exhibited a normal tertiary response. Mice similarly immunized on days 1 and 10 and given drugs on day 14 were challenged on day 15 with up to 3.5 x 10⁸ viable Moloney virus-induced lymphoma cells of BALB/c origin. Despite H-2 incompatibility, all nonimmune control mice developed ascites and died, whereas all mice immunized but not given drug failed to develop ascites. By contrast, 17 of 34 immunized mice given CY (180 mg/kg) and 7 of 34 given BCNU developed ascites. The ascites eventually regressed. The results show that CY and BCNU can suppress a secondary cellular immune response.

6288 HUMORAL AND CELL-MEDIATED IMMUNE RESPONSE IN PATIENTS WITH MALIGNANT MELANOMA. I. *IN VITRO* LYMPHOCYTE REACTIVITY TO PHA AND ANTIGENS FOLLOWING IMMUNIZATION. (Eng.) de Gast, G. C. (Univ. Hosp. Oostersingel 59, Groningen, The Netherlands); The, T. H.; Koops, H. S.; Huiges, H. A.; Oldhoff, J.; Nieweg, H. O. *Cancer* 36(4):1289-1297; 1975.

In vitro lymphocyte reactivity to test antigens was studied in 61 patients with malignant melanoma. Thirty-one of these patients had localized disease; thirteen, regional metastases; ten, distant lymph node or skin metastases; and seven, visceral metastases. Diphtheria and tetanus toxoid were injected *im* in the deltoid region, and α-hemocyanin of *Helix*

pomatia was given, *sc*. Following immunization, *in vitro* lymphocyte reactivity to the three antigens was studied in the presence of autologous serum, in addition to lymphocyte reactivity to phytohemagglutinin (PHA). The patients with visceral metastases had a lowered lymphocyte reactivity to PHA compared with controls and patients with other stages; they also had a low reactivity to the test antigens. All these patients showed tumor progression or died from metastatic disease. Between the other stages there was no difference in lymphocyte reactivity to the test antigens or PHA. No correlation between lymphocyte reactivity to PHA and the subsequent course of the disease could be demonstrated in these 54 patients. However, nine of the 14 patients without any lymphocyte reactivity to the three antigens showed tumor recurrence or progression, against one of the 40 patients with positive lymphocyte reactivity to one, two, or three antigens. A suppressive effect of autologous serum on lymphocyte reactivity could be found only in one of 20 patients with a low reactivity to PHA or antigens. Defects in lymphocyte function are related to subsequent tumor growth in patients with malignant melanoma.

6289 THE EFFECT OF SPLENECTOMY ON TUMOR IMMUNITY AND THE METASTATIC SPREAD OF A MURINE RETICULUM CELL SARCOMA. (Eng.) Faraci, R. P. (Surgery Branch, Natl. Cancer Inst., Bethesda, Md.); Marrone, J. C.; Lesser, G. R.; Ketcham, A. S. *Panminerva Med.* 17(3):59-64; 1975.

The effect of splenectomy on the immune response of adult female mice to a methylcholanthrene-induced sarcoma (MCA-10) and on the metastatic spread of a reticulum cell sarcoma (RCS) was evaluated. In experiment I, 200 C57BL/6N mice were injected (*im*, right leg) with 10⁶ MCA-10 sarcoma cells. When the tumors reached one centimeter in diameter, the legs were amputated. Three days later, 100 mice were splenectomized, and one week later all mice were divided into five groups receiving 10³-10⁷ tumor challenges. A greater number of tumors appeared initially in the splenectomized animals, but with time, tumor incidence in the non-splenectomized mice approached that of the former group; at a challenge dose of 10⁴, the splenectomized group showed the highest incidence (64%) of kidney metastases, while the group with two spleens had the lowest (8%). The authors conclude that the removal of the spleen in the mouse results in a significant loss of immunity to MCA-10 sarcoma. In addition, the spleen attracts the RCS and appears to protect the host against systemic metastases of the RCS. Thus, the spleen exerts a protective effect in limiting visceral metastases of a lymphoma in mice.

6290 IMMUNITY TO MAREK'S DISEASE INDUCED BY GLUTARALDEHYDE-TREATED CELLS OF MAREK'S DISEASE LYMPHOBLASTOID CELL LINES. (Eng.) Powell, P. C. (Houghton Poultry Res. Station, Houghton, Huntingdon, Cambridge PE17 2DA, U.K.). *Nature* 257 (5528):684-685; 1975.

Evidence was sought for anti-tumor immunity in experimentally immunized birds, immunity induced by glu-

taraldehyde-treated cells of Marek's disease (MD) lymphoblastoid cell lines. Groups of 25 HPRS Rhode Island Red chickens were immunized with glutaraldehyde-inactivated tumor cells, infected lymphocytes, normal lymphocytes, lymphoblastoid cell lines or infected chick kidney cells (CKC). One control group received no treatment, another was inoculated with standard MD vaccine (HVT). Mortality was observed until the birds were 230 days old. The χ^2 test was used to compare mortality rate in the various groups. As expected, birds which had been vaccinated with HVT or immunized with inactivated MDV infected CKC's were significantly better protected against MD. The resistance to MD may proceed by a two-step mechanism. The restriction of virulent virus infection brought about by vaccination may result in a much reduced incidence of malignant transformation of T lymphocytes, by reducing the probability of appropriate virus-cell interactions leading to neoplastic transformation. These transformed cells may be the target for the second step, the rejection of neoplastic cells. Further research must be done; the nature of the tumor specific antigens and the role played by MDV in inducing their appearance remain unknown.

- 6291 ALTERATIONS IN GRAFT-VERSUS-HOST REACTIVITY AND PERIPHERAL LEUKOCYTES IN MICE AFTER ERYTHROPOIETIN TREATMENT. (Eng.) Kinnamon, K. E. (Walter Reed Army Inst. Res., Washington, D.C. 20012); Blackwell, L. H.; Ledney, G. D. *Exp. Hematol.* 3(4): 234-243; 1975.

To determine whether the previously demonstrated abnormal immune response in hypoxic mice, together with the neutrophilia and decreased lymphocytes and monocytes seen in persons subjected to high altitudes, might both be related to increased levels of erythropoietin (EP), experiments were carried out with adult CBA and C57BL/6 mice to determine if exogenously administered EP might elicit changes in immune response and observable alterations in hematopoiesis. For comparison, changes resulting from administered rabbit antimouse thymus serum (ATS) were also investigated. Sterile saline and normal rabbit serum were used as control test substances. Tests for changes in immune response were carried out by measuring the increase in spleen weights of 1-4-day-old (CBA x C56BL/6) F_1 mice after they were injected i.p. with 20×10^6 cells taken from spleens of EP- or ATS-treated CBA or C56BL/6 mice. Tests for alterations in hematopoiesis were carried out by differential leukocyte counts on circulating blood of treated and control CBA and C56BL/6 mice. Treatment of the test mice on 4 consecutive days with either EP or ATS resulted in a significant reduction in antigenic reactivity of spleen cells, in lymphopenia and, in most instances, a neutrophilia and a variable monocytopenia. Similar alterations in cell types were also observed following EP- or ATS-treatment of mice rendered polycythemic by use of selectively permeable dimethyl silicone rubber membrane cages. These findings, along with results of histologic analyses of spleens of the treated animals, supported the idea that there is an inverse relationship between the cells committed to differentiate along the lymphoid

cell line and those committed along myeloid cell lines. Further, the data were consistent with the "carrying capacity" concept regarding the stem cell microenvironment and supported the monophyletic theory of cell differentiation.

- 6292 IMMUNOSUPPRESSION INDUCED *IN VITRO* BY MASTOCYTOMA TUMOR CELLS AND CELL-FREE EXTRACTS. (Eng.) Kamo, I. (Albert Einstein Med. Cent., Philadelphia, Pa.); Patel, C.; Kately, J.; Friedman, H. *J. Immunol.* 114(6):1749-1756; 1975.

The nature and mechanism of suppression of antibody formation by mastocytoma cells in mice was studied. Female DBA/2 and C57BL/6 mice, as well as B₆D₂F₁ hybrids were used. When spleen cells from mastocytoma-bearing mice were incubated *in vitro* and immunized with SRBC, suppressed anti-SRBC responses occurred. Similar responses occurred when mastocytoma cells, their cell-free homogenates, or ascitic fluid from tumor-bearing mice were added to spleen cell cultures from normal mice immunized *in vitro* with the SRBC. Immunosuppression was observed when the mastocytoma cells were separated from the normal cells by 0.4- μ nucleopore membranes, but did not occur when the separation was by dialysis membranes. The suppressive activity of the cell-free homogenates was retained in supernatant ultracentrifugates, but was abolished by heating. Suppression was most evident when mastocytoma extracts were added to cultures of normal splenocytes at the time of *in vitro* immunization and culture initiation. Washing the cultured cells and addition of fresh medium did not reverse the response. Immunosuppression also occurred when mastocytoma extracts were incubated with spleen cells from allogenic tumor-resistant C57BL/6 mice. These data indicate that mastocytoma cells release an immunosuppressive substance(s) *in vitro* as well as *in vivo* and that this substance is soluble, heat sensitive and non-dialyzable. The need for more detailed information to determine if the inhibitory factor(s) has an important immunoregulatory role in terms of the malignant process *per se* is discussed.

- 6293 HEAVY CHAIN-PRODUCING VARIANTS OF A MOUSE MYELOMA CELL LINE. (Eng.) Morrison, S. L. (Albert Einstein Coll. Med., Bronx, N.Y.); Scharff, M. D. *J. Immunol.* 114(2):655-659; 1975.

The P3 cell line, adapted to culture from a MOPC-21 mouse myeloma tumor, was mutagenized with either the acridine half-mustard ICR-191 (1 μ g/ml) or with N-methyl-N'-nitro-N-nitrosoguanidine (5 μ g/ml). The cultures contained 5×10^5 cells/ml. Eleven variants that produced only heavy chains were isolated. Cytosolic lysates were prepared from 14 C-amino acid-labeled variant cells. Immune precipitates were made, and then electrophoresed on 5% acrylamide-sodium dodecyl sulfate (SDS) gels. Three radioactive peaks were observed, but none was found to correspond to light chains. Reduction and alkylation of the heavier radioactive peaks and then re-analysis on SDS gels still showed no light chains when compared to parent P3 light chains. The heavy chains present

were shown to be similar, both in molecular weight and by peptide maps, to the parental P3 heavy chains. Pulse-chase experiments showed that the heavy chains in these variants dimerized and were stable intracellularly up to 24 hr. However, the heavy chains and heavy chain dimers were not secreted. These studies show that in the P3 cell line, the synthesis of heavy chains can continue in the absence of detectable light chain synthesis.

- 6294 QUANTITATION OF ELUTABLE IMMUNOGLOBULIN G (7S) FROM FRESH MALIGNANT HUMAN TUMOR-CELL SURFACES. (Eng.) Krishnan, E. C. (Univ. of Kansas Medical Center, Kansas City, Kans.); Jewell, W. R. *Transplant. Proc.* 7(1/Suppl. 1):541-544; 1975.

Elutable immunoglobulin G (IgG) from 11 different human malignant tumor cells was quantified by radio-immunoassay techniques. Tumor-cell-surface IgG was eluted from fresh tumor cells with pH 2.6 glycine buffer. Fresh tumor cells contained measurable amounts of IgG on their surfaces, whereas cultured cells contained only trace amounts. The amount of IgG found by direct measurement on cells varied from 85 to 800 ng/10⁶ cells; however, considerable amounts of protein were usually lost in the elution procedure. The eluates contained IgG, IgM, and albumin; α_2 macroglobulin was not found. The authors suggest that an antigen-antibody complex could be formed in the vicinity of tumor cells, attached to the cells by the Fc-receptor mechanism, and prevent cell-mediated cell destruction by covering tumor antigen sites.

- 6295 Gm AND Inv MARKERS IN WHOLE MYELOMA SERA IN AN IRISH POPULATION. (Eng.) Blake, P. J. (Central Immunology Lab., Trinity Coll., Dublin 2, Ireland); Greally, J. F. *J. Immunogenet.* 2(3):147-149; 1975.

A survey of the distribution of genetic markers of the Gm and Inv systems in the sera of patients with myeloma was carried out on an Irish population. A total of 136 patients were in the experimental group, 294 patients formed the control group. Immunoglobulin G (IgG) heavy chain antigenic determinants in humans were termed Gm markers and the light chains of K type only had factors designated Inv. The anti Gm, anti-D/Gm, anti-Inv and anti-D/Inv sera together with positive and negative control sera were of human origin. The method used for the determination of Gm type was hemagglutination inhibition test. ORh-positive erythrocytes (CDe/cDE) were sensitized with anti-D/Gm sera having the required marker. In each test, controls were included for: 1) sensitized erythrocytes, 2) non-specific agglutination by patient's serum, 3) positive and negative agglutinating systems, and 4) positive and negative serum. The frequency of the individual classes of myeloma was IgG 61%, IgA 23.5%, IgM 15.5%. In the myeloma sera, the values were found to be Gm(+1) 46%, Gm(+2) 26% and Gm(+12) 96%. Gm(+4), however, showed a frequency of 41% which was less than the expected 90%. The main difference between the normal population and that

of myeloma patients was the relatively low frequency of Gm(+4) in the myeloma sera. As part of a continuing study, a number of normal sera will be investigated with specific reagents and methods to determine if any abnormal ratios of the Gm markers are obtained.

- 6296 γ G-GLOBULIN PRODUCTION AND LIGHT-CHAIN METABOLISM IN PATIENTS WITH METASTATIC CANCER. (Eng.) Waterhouse, C. (Univ. Rochester Sch. Med. Dent., N.Y.). *Cancer Res.* 35(4):987-990; 1975.

γ G-Globulin and excess light-chain metabolism were studied in eight subjects with progressive metastatic malignant disease by determining the plasma radioactivity curves following the administration of appropriately labeled substances. In addition to the plasma die-away curves, which required about three weeks for full expression for γ -globulin, but only 3-4 days for light-chain, urinary excretion of the label from metabolized protein was determined. The data are compared to similar studies in control individuals. The metabolism of excess light chain was similar to normal in all respects. The total synthesis of γ G-globulin was increased with a mean value about twice normal. The mean survival time of a circulating immunoglobulin molecule was short, indicating rapid loss from the system. Other aspects of immunoglobulin metabolism were similar to normal with a normal percentage of the labeled protein appearing in the urine, suggesting no abnormality in the utilization pattern but simply an increased rate of turnover. The capability of malnourished patients with cancer to produce large quantities of immunoglobulin is not specific for this disease, since similar patterns may be seen in response to infections in protein-depleted individuals. However, there is the possibility that the cancer itself acts as an inciting agent in these subjects. Such sustained protein synthesis may place an additional burden on already compromised host metabolism.

- 6297 PARTIAL CHARACTERIZATION OF THE SHIFT FROM IgG TO IgA SYNTHESIS IN THE CLONAL DIFFERENTIATION OF HUMAN LEUKEMIC BONE MARROW-DERIVED LYMPHOCYTES. (Eng.) Rudders, R. A. (Tufts Univ. Sch. Medicine-New England Medical Center Hospital, Boston, Mass. 02111); Ross, R. *J. Exp. Med.* 142(3):549-559; 1975.

An unusual B-cell proliferation was noted in a 54-yr-old man with a 3-yr history of chronic lymphocytic leukemia (CLL). This proliferation was characterized by the presence of two separate populations of CLL cells staining on the surface and in the cytoplasm for either IgG(κ) or IgA(κ). Utilizing an idiotypic antiserum prepared from the associated serum monoclonal IgG(κ) protein, the idiotype was detected on the surface and in the cytoplasm of both the IgG- and IgA-bearing cell populations. These observations are consistent with a common clonal origin and a switch mechanism involving IgG and IgA synthesis. Sequential-labeling of

surface and intracellular immunoglobulins with antisera conjugated to opposite fluorochromes documented the progressive maturation of the IgG-bearing cell population to recognizable plasma cells and the failure of terminal differentiation of the IgA-bearing cell population at a level before morphologically distinct plasma cells. The distribution and pattern of surface and cytoplasmic IgG and IgA staining in individual cells suggest that the direction of switching is from IgG to IgA synthesis. The demonstration of shared idiotypic specificity between the IgG- and IgA-bearing populations is consistent with a transition in immunoglobulin heavy chain synthesis resulting from an alteration in the C_H gene. It is concluded that certain CLL clones may manifest a switch from IgG to IgA synthesis at a level of B-cell differentiation which encompasses both the B lymphocyte and the Ig-synthesizing plasma cell.

- 6298 MECHANISMS OF SPECIFIC AND NON-SPECIFIC TUMOUR IMMUNITY AFTER AZATHIOPRINE TREATMENT OF MICE. (Eng.) Purves, E. C. (St. Mary's Hosp. Medical Sch., London W2 1PG England). *Clin. Exp. Immunol.* 22(2):348-358; 1975.

The ability of phagocyte-depleted spleen cells to lyse chicken erythrocytes (CRBC) in the presence of antibody was measured in mice (female C57Bl, BALB/c, DBA/2) treated with azathioprine. Single doses of the drug had no effect on this ability when measured on the day after administration. A four-day course of 80 mg/kg/day of the drug reduced splenic antibody-dependent cell-mediated cytotoxicity (ADCC) to 20% of the control value for phagocyte-depleted spleen cell populations. It reduced neither antibody responses nor the development of cytotoxic cells following subsequent immunization with an allogeneic tumour. The 4-day drug treatment increased the ADCC of whole-spleen cell populations 4.5-fold. The whole populations had only 20% of the level of cytotoxic cells as phagocyte-depleted populations did. Splenic phagocytosis and phagocyte-mediated ADCC were both slightly enhanced following drug treatment. The implications are that the major antibody-dependent cytotoxic cell in phagocyte-depleted mouse spleen is normally in a state of proliferation, and plays no important role in antigen recognition.

- 6299 HUMAN ENDOMETRIAL CARCINOMAS SERIALLY TRANSPLANTED IN NUDE MICE AND ESTABLISHED IN CONTINUOUS CELL LINES. (Eng.) Merenda, C. (Dept. Biochemistry, Univ. Lausanne, Lausanne, Switzerland); Sordat, B.; Mach, J. P.; Carrel, S. *Int. J. Cancer* 16(4):559-570; 1975.

Attempts were made to establish long-term tissue culture lines from five endometrial adenocarcinomas grown in nude mice. The effects of medroxyprogesterone acetate were also studied, both on tumor explants growing in nude mice and on the same tumor cells cultivated *in vitro*. Three of the five endometrial carcinomas were successfully grafted into

nude mice (BALB/c/nu/nu). Two of these tumors could be maintained by serial transplantation. The morphological characteristics displayed by the grafted tumors were comparable to those of the original carcinomas. Permanent cell lines were established from these two tumors. Reinjection of cells grown *in vitro* into nude mice produced nodules of identical histology as compared to original solid transplants. Forty-six female nude mice were either used as untreated controls or given two ip injections of 5 mg (0.1 ml) medroxyprogesterone on days 3 and 10 after tumor grafting. This represented an average of 0.4 mg/g body weight. The tumors were measured twice a week; after 17 days the animals were killed and the mean tumor diameters and weights were obtained. Medroxyprogesterone (0.5, 1, 4, and 10 µg/ml) was also added to cultured tumor cells. These treatments did not produce any significant effect on tumor cells, either *in vitro* or *in vivo*, for the two endometrial carcinomas. After medroxyprogesterone administration, a slight but nonsignificant growth inhibition of the tumor cells *in vitro* was observed and the tumor transplants *in vivo* did not appear to be influenced. The experiments illustrate the possible use of this model for testing potential anti-cancer agents.

- 6300 STUDIES ON HUMAN IgD MYELOMA PROTEINS: CARBOHYDRATE COMPOSITION OF INTACT PROTEINS AND SOME PROTEOLYTIC FRAGMENTS. (Eng.) Jeffers, R. (Univ. Birmingham Medical Sch., Birmingham B15 2TJ England); Butwell, A. J.; Clamp, J. R. *Clin. Exp. Immunol.* 22(2):311-315; 1975.

The carbohydrate composition of three immunoglobulin D (IgD) myeloma proteins were identified and the results were compared with data from the literature to ascertain the degree of variability within this Ig class. IgD proteins were isolated from myeloma sera by gel-filtration and ion-exchange chromatography. Purity was controlled by Ouchterlony and immunoelectrophoresis. IgD was fragmented by papain digestion in the absence of cysteine into Fab δ and Fc δ fragments; Fc δ was then fragmented by trypsin digestion. Carbohydrate analyses were determined by gas-liquid chromatography. All of the carbohydrate content was found in the Fc δ fragment; however, antiserum raised to Fab δ fragment also had strong precipitating antibody to the Fc δ fragment due to a low level of contamination of the Fab δ fragment with a further papain digestion fragment of the Fc δ . The carbohydrate content of the three IgD proteins varied with the total carbohydrate accounting for 9 to 18% of the IgD protein. The mean value as whole residues/molecule of protein for four IgD proteins was one residue of fucose, 23 of mannose, 16 of galactose, 17 of N-acetylglucosamine, 11 of N-acetylgalactosamine, and 16 of N-acetylneuraminic acid. The four proteins had similar fucose, mannose, and N-acetylglucosamine contents; the individual variations in carbohydrate content were due to small differences in galactose, N-acetylgalactosamine, and sialic acid contents. N-acetylgalactosamine was contained in the heavy carbohydrate moiety attached within the "hinge" region of the heavy chain.

IgD is therefore similar to IgA₁ in having a high carbohydrate content and in containing *N*-acetylgalactosamine.

- 6301 NATURAL CYTOTOXIC REACTIVITY OF MOUSE LYMPHOID CELLS AGAINST SYNGENEIC AND ALLOGENEIC TUMORS. II. CHARACTERIZATION OF EFFECTOR CELLS. (Eng.) Herberman, R. B. (Nat'l. Cancer Inst., Bethesda, Maryland); Nunn, M. E.; Holden, H. T.; Lavrin, D. H. *Int. J. Cancer* 16(2):230-239; 1975.

Studies were performed to characterize the effector cells responsible for natural cytotoxicity of mouse lymphoid cells against a variety of syngeneic and allogeneic tumor lines. Highly cytotoxic spleen cells from normal nude mice were used for most of the experiments. Only a small proportion of the reactivity was affected by treatment with anti- θ -serum plus complement. Macrophages did not appear to be responsible for the reactivity, because treatment with carbonyl iron/magnet or carrageenan did not affect the levels of cytotoxicity. Passage over nylon columns resulted in a considerable increase in activity, indicating that the effector cells were nonadherent. The active cells did not have receptors for immunoglobulin or complement since removal of cells with these receptors by columns or monolayers containing SRBC complexes or SRBC complement complexes did not remove activity. Antibody-dependent cell-mediated cytotoxicity was ruled out as the mechanism for natural cytotoxicity, because aggregated gamma globulin and a potent antiimmunoglobulin reagent did not inhibit reactivity, and because no role for humoral factors could be demonstrated. The natural effector cell was found to be labile at 37 C, losing much of its activity after four hours. Since no surface markers could be detected on the effector cells, and because the mechanism for cytotoxicity appeared distinct from others previously described, it is proposed that the natural cytotoxicity against mouse tumor cells is mediated by a unique subpopulation of lymphoid cells, which are tentatively designated *N*-cells.

- 6302 IMMUNOSURVEILLANCE OF NATURALLY OCCURRING FELINE LEUKEMIA. (Eng.) Essex, M. (Harvard Univ. Sch. Public Health, Boston, Mass. 02115); Sliski, A.; Cotter, S. M.; Jakowski, R. M.; Hardy, W. D., Jr. *Science* 190(4216):790-792; 1975.

Immunosurveillance of naturally occurring feline leukemia was performed. Resistance to tumor development or tumor progression, and humoral antibody response to the feline oncornavirus-associated cell membrane antigen (FOCMA) was found in cats inoculated with feline sarcoma virus (FeSV) or feline leukemia (FeLV). Pet cats with spontaneous leukemia or lymphoma had low or negative FOCMA antibody titers. Control healthy cats from leukemia cluster households had both a high FOCMA antibody titer and a high frequency of viremia with FeLV. A total of 51 cats from a single private household were followed having been identified as a leukemia cluster.

FOCMA antibody and FeLV antigen levels were determined every four months over a two and a half year period. Control cats of similar genetic background were brought up separately, isolated from FeLV and FeSV and showed no FOCMA antibody titer. Eight of the 51 cats which developed leukemia recorded a FOCMA antibody titer higher than two when checked before the clinical onset of leukemia, whereas the other cats which remained healthy had titers of four and higher. The mean antibody titers for cats that remained healthy were more than five times higher than the comparable values for the cats which developed leukemia. These results are interpreted as supporting the concept of immunosurveillance in an outbred species of mammal.

- 6303 IMMUNE RESPONSE TO A SYNGENEIC MAMMARY ADENOCARCINOMA. I. COMPARISON OF KINETICS OF TUMOR CELL GROWTH AND CYTOTOXIC RESPONSES IN SYNGENEIC AND ALLOGENEIC RATS. (Eng.) Fortner, G. W. (Stanford Univ. Medical Center, Stanford, Calif. 94305); Kuperman, O.; Lucas, Z. J. *J. Immunol.* 115 (5):1269-1276; 1975.

Mammary adenocarcinoma MT 13762A, originating in 7, 12-dimethylbenz(a)anthracene-treated Fischer 344 rats, was studied and in both allogeneic and syngeneic hosts. Tumor growth and lymphocyte cell-mediated cytostasis (L-CMC) were quantitated. The tumor was converted to an ascites form (MTA) by ip passage. For use as target cells in L-CMC assays, the MTA was grown in monolayer culture (MTM). Immune cells were obtained from Fischer 344 rats immunized with ¹³⁷Cs-irradiated MTA cells. Microcytotoxicity assays were based on incorporation of ⁸⁶Rb by viable target MTC cells following incubation with immune spleen lymphocytes. Tumor cells were also tested for agglutination by concanavalin A (Con A). The MT 13762A was weakly immunogenic in syngeneic animals; this was indicated by death after injection of only ten MTA cells, and by lack of transplantation immunity after injection of irradiated MTA cells. High dosage *in vivo* passage of MTA revealed two cell types. One (sublines MTA-met and MTM) grew slowly as a solid tumor, was rejected by allogeneic animals, and permitted survival of syngeneic hosts for 18-24 days. The other (subline MTA-HP) grew rapidly in ascites form, even in allogeneic animals, and allowed survival for 15 days in syngeneic animals and for 29 days in allogeneic animals. Presumptive evidence for antigens common to both cell types was found when allogeneic animals immune to MTA rejected the previously lethal MTA-HP. The results suggest that MTA-HP antigens common to those of MTM might be covered or altered to become nonimmunogenic. The CMC assay of spleen cells further demonstrates common antigens, since spleens from animals injected with either MTA or MTA-HP contained cells cytotoxic for MTM and the kinetics of cytotoxic lymphocytes were the same for both MTA and MTA-HP. The *in vivo* rejection of tumor did not correlate, however, with the *in vitro* assay of CMC; this was demonstrated by the fact that tumor growth stopped after four days in allogeneic animals, a time at which there was negligible demonstrable CMC. In syngeneic animals, where exponential tumor cell growth kills the host

in 12 days, the kinetics of spleen cell cytotoxic activity paralleled that found in allogeneic animals. Although no correlation could be shown between kinetics of CMC and *in vivo* tumor rejection, this did not rule out a participation of spleen cells in tumor rejection, either directly or in cooperation with other cells.

- 6304 HISTOPATHOLOGICAL STUDIES ON EXPERIMENTALLY INDUCED PULMONARY ADENOMATOSIS IN GUINEA-PIG LUNGS. (Eng.) Torikata, C. (Keio Univ., Sch. Medicine, Tokyo, Japan); Takeuchi, H.; Yamaguchi, H.; Kageyama, K. *Acta Pathol. Jpn.* 25 (5):555-563; 1975.

The induction of diffuse pulmonary fibrosis resembling that found in human lungs was studied in experimental animals. When guinea pigs were injected with bovine serum albumin and antbovine serum albumin iv and continuously exposed to a 40%-60% oxygen-rich atmosphere, diffuse pulmonary fibrosis occurred in the lungs of many 2 to 3 mo later. After the 100th experimental day, multiple foci of pulmonary adenomatosis occurred in all animals. The morphology was similar to that of the Jaagsiekte lesion. Electron microscopic observations revealed that these hyperplastic cells originated from type II pneumonocytes.

- 6305 LACK OF CORRELATION BETWEEN GROWTH CHARACTERISTICS, AGGLUTINABILITY BY PLANT LECTINS AND THE MALIGNANT PHENOTYPE. (Eng.) Berman, L. D. (Boston Veterans Administration Hosp., Boston, Mass. 02130). *Int. J. Cancer* 15(6):973-979; 1975.

The concept that lectin agglutination of animal cells is specific for the transformed state was tested in a defined cellular system where malignant expression could be modified by experimental means. The lectins studied were concanavalin A (Con A) and wheat-germ agglutinin (WGA). Agglutination assays were carried out on single cell suspensions of 4×10^5 viable cells in 0.2 ml phosphate-buffered saline containing 0.1% gelatin, to which 0.05 ml lectin was added (0.06% Con A; about 1% WGA). Transplantability of hamster-derived cells was tested by sc injection of ten-fold doses of cells into random-bred Syrian hamsters. Growth in soft agar was tested in medium containing 0.3% agarose. Saturation density was tested by light seeding of cells on Petri dishes, growing to confluency, and counting of harvested cells. Con A and WGA agglutinated a variety of normal hamster cells as well as a number of lines of transformed or tumor cells. The normal cells included preparations from embryos and neonatal organs, and the spontaneous line, BHK-21 C13. For a fuller study, three sublines of BHK cells were studied. A "flat revertant", selected by FUDR treatment, grew to diminished saturation density and failed to produce colonies in soft agar, in contrast to the parent line. Yet, it was only minimally less tumorigenic and less agglutinable than the parent line. Lines derived from one and four consecutive *in vivo* tumor passages showed in-

creased tumorigenicity and growth in soft agar when compared to the parent line. At the same time, agglutinability of these lines was not significantly increased. The results indicated, therefore, that tumorigenicity may correlate poorly with growth characteristics and agglutination by plant lectins.

- 6306 IMMUNE FACTORS IN LEUKEMOGENESIS. (Eng.) Cornelius, E. A. (Yale Univ. Sch. Medicine, New Haven, Conn. 06510). *Proc. Int. Cancer Congr.* 11th. Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 285-289.

The effect of alteration of immune function by thymectomy (Tx) or graft *vs* host reaction (GVHR) on tumor induction was studied in mice. (BA)F₁ mice were thymectomized within 24 hr of birth and four to eight day old mice were given 0.15 ml of a 20% w/v tumor suspension i.p. Tumor incidence was based on clinical diagnosis corroborated by histological studies. Tx (BA)F₁ mice observed over a 24-month period were deficient in cellular immune function and demonstrated a high incidence of lymphomas and other lesions as shown by tumor and skin grafts, and delayed hypersensitivity skin tests. These results confirmed previous studies that revealed a relation between thymus function, immunological deficiency, and autoimmunity. The transplanted tumor grew more readily in Tx mice than in normal controls; by day 56, 35 out of 36 Tx mice had died as compared to seven of the 25 controls. One yr after grafting, nine of ten of Tx (BA)F₁ mice still accepted the (C57BL/6 x A)F₁ skin grafts as compared to only one of the ten normal controls. Tx mice also showed a decreased response to *M. butyricum*, revealing an impaired T-cell response. Chronic GVHRs were induced in young adult F₁ hybrid mice by i.p. injection of spleen cells from parental strain donors: A→(BA)F₁ by two injections of 100×10^6 cells, one month apart; B→(SB)F₁ by three injections of 250×10^6 cells, one month apart; and S→(SB)F₁ by five injections of 7×10^6 cells given at weekly intervals. In the model A→(BA)F₁, the cumulative tumor incidence of reticulum cell sarcomas increased to 53% by 16 months compared to a 5% increase in control mice. The mean duration of the GVHR was 13.7 months for donor type tumors and 2.1 months for host type tumors. In the model B→(SB)F₁, GVHR was mild, but all F₁ mice developed lymphomas by four months; all tumors were of the donor type. In S→(SB)F₁, two of 16 mice died on day 33, and by day 40, all the remaining F₁ mice developed anaplastic reticulum cell sarcomas. All control (SB)F₁ mice receiving frozen and thawed spleen cells also developed lymphomas in 40 days. In comparing different strain combinations, the authors conclude that tumor inducibility was not related to the clinical origin of the GVHR onto the presence or severity of nonlymphoid tissue pathology. These experiments provide the first demonstration of the induction of donor type tumors by GVHR in F₁ hosts not modified by prior irradiation. The S→(SB)F₁ model is unique because of the low donor cell dosage, high yield of tumors, and extremely short latent period for tumor induc-

tion. Additional irradiation experiments demonstrated that (SB)F₁ mice are not uniquely susceptible to all oncogenic agents.

- 6307 MICROMETHODS FOR INDUCTION AND ASSAY OF MOUSE MIXED LYMPHOCYTE REACTIONS AND CYTOTOXICITY. (Eng.) Simpson, E. (Clin. Res. Cent., Harrow, England); Gordon, R.; Taylor, M.; Mertin, J.; Chandler, P. *Eur. J. Immunol.* 5(7):451-455; 1975.

A micro method that enables the study of the relation of mixed lymphocyte responses (MLR) and cytotoxicity is described. Induction of MLR and cytotoxicity was performed under identical conditions. The spleen cells of BALB/c mice served as responders; antigen was obtained from C57BL/10 (or BALB/c x C57BL/10)F₁ mice. The assay involves the addition of 0.2 ml of attacking cell suspension (BALB/c sensitized spleen cells) to 0.05 ml of ⁵¹Cr-labeled target cells (either C57BL/10 ascites tumor EL-4 or mitogen-induced blasts of C57BL/10 spleen in each well of a flat-bottomed microtest II plate). The plate is centrifuged lightly (500 rpm) for five minutes, incubated from 1-3 hr at 37 C, and then recentrifuged for ten minutes at 1,000 rpm. Maximum MLR of 5 x 10⁵ BALB/c responder spleen cells cultured with either 5 x 10² 2,000 rad-irradiated BALB/c spleen cells (controls), or 5 x 10⁵ 2,000 rad-irradiated (C57BL/10 x BALB/c)F₁ spleen cells (experimental), as measured by [³H]thymidine uptake, occurred at 72-96 hr. The maximum cytotoxic response was observed in 5-day-old cultures. T cells alone were found to be involved in the induction and expression of cytotoxicity by two experimental approaches: (a) when whole spleen and nylon-purified T cells from spleen were cultured with antigen, the addition of 2-mercaptoethanol to the medium during the induction phase enabled the sensitization of the T cell preparation only, and (b) treatment of sensitized spleen cells with anti-Thy 1.2 prior to the assay abolished their cytotoxic effect. The optimal range of irradiated F₁ cells that stimulated both MLR and cytotoxic responses was 0.25 x 10⁶ to 1.0 x 10⁶. Comparison of the target tissues demonstrated that EL-4 and mitogen-induced blasts were equally sensitive, indicating that the cytotoxic effect is directed at antigens expressed on each of these cell types. These experiments further support the view that MLR is a prerequisite for the development of the cytotoxic response. In addition, the data obtained from these experiments is suitable for linear regression analysis enabling quantitative comparisons.

- 6308 CYCLIC GMP AND LYMPHOCYTE PROLIFERATION: EFFECTS ON DNA-DEPENDENT RNA POLYMERASE I AND II ACTIVITIES. (Eng.) Johnson, L. D. (Sloan Kettering Inst. Cancer Res., New York, N.Y. 10021); Hadden, J. W. *Biochem. Biophys. Res. Commun.* 66(4): 1498-1505; 1975.

To determine the possible role of cyclic guanosine 3':5'-cyclic monophosphate (GMP) and Ca²⁺ on nuclear RNA synthesis, a study was made of the effects of

these two agents on specific RNA polymerase I and II activities in nuclei from both phytohemagglutinin (PHA)-stimulated and non-stimulated lymphocytes. Lymphocytes separated from heparinized venous blood were maintained in culture medium containing 10% fetal calf serum. The PHA was added to the lymphocyte cultures at a concentration of 0.0082 U/10⁶ cells. The nuclei were prepared by a hypotonic shock method. RNA polymerase activity was assayed by incubation of nuclei with four ribonucleoside triphosphates (one of them tritiated), isolation of acid-insoluble product, and counting of the product in Omnifluor with a liquid scintillation spectrometer. RNA polymerase I was assayed in the presence of Mg²⁺; RNA polymerase II was measured in the presence of Mn²⁺. α -Amanitin was used to demonstrate RNA polymerase I resistance and RNA polymerase sensitivity to the compound. The results showed that cyclic GMP in the presence of Ca²⁺ stimulates RNA polymerase I activity in lymphocyte nuclei isolated from both nonstimulated and PHA-stimulated lymphocytes. The optimum concentration of cyclic GMP required for increasing polymerase I activity was about 10-fold greater for stimulated lymphocytes than for nonstimulated lymphocytes. At the same time, cyclic GMP in the presence of Ca²⁺ decreases RNA polymerase activity in both nonstimulated and PHA-stimulated lymphocyte nuclei. It is suggested that cyclic GMP and Ca²⁺ represent intracellular components of a plasma membrane-to-nucleus "mitogen signal sequence", such as may be involved when lymphocytes respond to PHA or other lectins.

- 6309 ATP-ase ACTIVITY OF LYMPHOCYTES FROM PATIENTS WITH CARCINOMAS OF THE URINARY BLADDER. (Eng.) Ellegaard, J. (Marselisborg Hosp., DK-8000 Aargus C, Denmark); Traunberg, H.; Dorff, B. *Scand. J. Urol. Nephrol.* 9(2):105-109; 1975.

A study was undertaken to obtain information on the lymphocyte ATP-ase activity in patients with urinary bladder carcinomas of different stages of malignancy and to observe changes in lymphocyte ATP-ase activity after radical treatment of the tumors. The investigation included 26 patients with urinary bladder carcinomas, 17 control patients with non-malignant bladder disease, and 50 normal individuals. The ATP-ase assay was based on liberation of inorganic phosphate (P_i) from the substrate Tris-ATP. The ATP-ase activity in lymphocytes from the cancer patients was 143.1±55.3 nmoles P_i per mg protein per hr, which was significantly higher than the activity of 9.13±33.3 for normal subjects and 82.9±41.3 for non-malignant controls. There was, however, overlapping of low values for cancer patients with high values for normal subjects. Thus, in only 13/26 cancer patients were the values significantly higher than those for controls. A decline in ATP-ase activity was found in 14/17 patients re-investigated after treatment, while the activity remained unchanged in two and rose in one patient. No correlation was found between clinical tumor stage and lymphocyte ATP-ase activity, but the activity was closely correlated with histological grade of malignancy. The test for lymphocyte ATP-ase was suggested to be of diagnostic significance in cancer of the urinary

bladder, perhaps especially in tumors of low clinical, but high histological grade of malignancy.

- 6310 T AND B LYMPHOCYTES IN SPLEENS IN HODGKINS DISEASE [letter to editor]. (Eng.) Wagener, D. J. T. (St. Radboud Hosp., Univ. Nijmegen, Netherlands); Geestman, E.; Borgonjen, A. *Lancet* (1972):1378-1379; 1975.

The phytohemagglutinin (PHA) stimulation test was performed on peripheral blood lymphocytes in 17 Hodgkin's disease patients before, and ten days after splenectomy. PHA stimulation was not affected in Hodgkin's patients with pathological stages I and II but was significantly increased in those with stages III and IV. The relative proportions of T and B cells in the peripheral blood of 12 patients before and after splenectomy were measured by rosette formation. The proportion of E-binding lymphocytes was significantly diminished in seven patients with spleens weighing 240 g and more, whereas PHA-stimulated thymidine incorporation increased significantly. The proportion of EAC-binding lymphocytes also increased significantly in these patients. In patients with a splenic weight less than 200 g, no significant difference after surgery was observed. The decrease of E-binding lymphocytes in the cases with resected spleens of over 240 g may be due to the removal of the spleen containing many T lymphocytes. Response to PHA is not always decreased when the proportion of E-binding lymphocytes is decreased.

- 6311 THE SPECIFIC AND ENDOGENOUS MITOTIC INHIBITOR OF LYMPHOCYTES (CHALONE). (Eng.) Attalah, A. M. (Nat'l. Medical Center, Washington D. C. 20009); Sunshine, G. H.; Hunt, C. V.; Houck, J. C.* *Exp. Cell Res.* 93(2):283-292; 1975.

Aqueous extracts of various lymphoid tissues, but not of non-lymphoid tissues, contain a species-non-specific but cell-specific inhibitor of the transformation and DNA synthesis of PHA-stimulated human lymphocytes which is considered not cytotoxic and is reversible. This activity was found in similar molecular weight fractions from pure lymphocytes obtained in culture and would appear to be endogenous to the lymphocyte itself. PHA-stimulated normal lymphocyte cultures from the circulation of human volunteers were taken. The effect of chalone was studied upon the cultures of NC-37 diploid human B cell lymphoblasts. Molt T-cell-established leukemic lymphocytes, rat bone marrow, and HeLa cells to test their ability to incorporate ³H-thymidine into acid-insoluble DNA after 24 hr incubation. The specific and endogenous mitotic inhibitor did not appear to be a result of competitive lectin-binding, thymidine pool size dilution, phosphorylation, destruction of thymidine, or the direct immunosuppressive effects of thymidine upon row, and HeLa cells were tested for their ability to incorporate ³H-thymidine into acid-insoluble DNA after 24 hr incubation. The ultrafiltrates of spleen and lymph node extract inhibited DNA synthesis 99% in both PHA-stimulated and NC-37 lymphoblastic cell lines *in vitro*. The specific and endogenous mitotic inhibitor did not appear to be a result of competitive lectin-

binding, thymidine pool size dilution, phosphorylation, destruction of thymidine, or the direct immunosuppressive effects of thymidine upon the lymphocytes themselves. Rather it appeared to be a result of the effects of a protein contained in the crude ultrafiltrate from lymphoid tissues whose properties correspond to those originally described by Bullough & Laurence for a 'chalone'. The chalone activity from thymus would appear to be specific for T cells rather than B cells.

- 6312 LYMPHOCYTE POPULATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA AND HODGKINS'S DISEASE. (Ger.) Cohnen, G. (Medizinischen Universitätsklinik, 43 Essen 1, Hufelandstrasse 55, Germany). *Fortschr. Med.* 93(2):71-76; 1975.

The T and B lymphocytes in the peripheral blood of normal subjects and of patients with chronic lymphocytic leukemia (CLL) and Hodgkin's disease were studied using phytohemagglutinin (PHA) and pokeweed mitogen (PM). Circulating lymphocytes in CLL were found to consist predominantly of B lymphocytes and of a residual population of normally reactive T and B cells. Reduced activity of lysosomal enzymes was observed. Reduced T lymphocyte count was found in most patients with Hodgkin's disease. Reduced T lymphocyte count and increased B lymphocyte count were observed primarily in the advanced stages of this disease. The *in vitro* reactivity of the lymphocytes after stimulation with PHA was reduced mainly in the generalized form of the disease. There may be a functional impairment of the cells, which in some cases seems to involve both T and B lymphocytes. The quantitative and qualitative changes of the T lymphocyte system manifest themselves in a reduction of the cellular immunity of patients with Hodgkin's disease.

- 6313 ULTRASTRUCTURAL COMPARISON OF THE CELL COAT IN NORMAL AND CHRONIC LYMPHOCYTIC LEUKAEMIC BLOOD LYMPHOCYTES BY CONCAVALIN A LABELLING AND CATIONIC STAINING. (Eng.) Calman, F. (91 boulevard de l'Hopital, 75635 Paris Cedex 13, France). *Pathol. Eur.* 10(3):203-214; 1975.

The ultrastructures of cell coats of normal and chronic lymphocytic leukemic (CLL) blood lymphocytes were compared by several cytochemical techniques. The CLL lymphocytes were obtained from 21 patients; the normal lymphocytes, from 12 healthy subjects. Lymphocytes prepared from heparinized venous blood were fixed in 2% glutaraldehyde and examined after staining with colloidal iron, ruthenium red, or colloidal thorium. They were also examined after labeling with concanavalin A (Con A), using peroxidase staining to reveal the Con A. Results with Con A showed that, except for one patient, the thickness of the precipitate was the same for the pathological as for the normal lymphocytes. With colloidal iron, there was a slightly reduced intensity for all patients. With ruthenium red, there was a more marked decrease in staining, some patients showing no staining what-

ever. With colloidal thorium, four of the 12 patients studied showed normal staining, three showed a slight decrease, and four showed complete fading of staining. For any given technique, the staining intensity of the cell coat was the same for all of the cells within a sample. The findings signified a modification of anionic reactive sites. Aside from the differences in staining of cell coats of lymphocytes from different test subjects, no cytological differences between lymphocytes of normal and leukemic subjects could be observed. In no case could a correlation be found between the alteration in staining and the clinical condition or the severity of the disease.

- 6314 INDUCTION OF 16 α -HYDROXYLASE IN CULTURED HUMAN LYMPHOCYTES. (Eng.) Muijsson, I. E. (Dept. Biology and Basic Health Sciences, North Texas State Univ., Denton, Tex.); Coomes, M. L.; Cantrell, E. T.; Anderson, D. E.; Busbee, D. L. *Biochem. Genet.* 13(7/8):501-509; 1975.

Lymphocytes were grown for 72 hr in the presence of mitogenic agents and exhibited a nine-fold increase in 16 α -hydroxylase activity over a 24-hr period following the addition of 17 β -estradiol as an inducing agent. The major metabolite of 17 β estradiol produced by induced lymphocytes showed a chromatographic mobility indistinguishable from that of estriol. The enzyme activity was not increased above basal level during induction in the presence of cycloheximide, indicating a requirement for protein synthesis associated with enzyme induction. Enzymatic activity increased linearly with cell numbers, was inhibited by CO, and exhibited no induced increase in the presence of cycloheximide. A population survey indicated that about 68% of a randomly selected Caucasian group would be essentially uninducible for 16 α -hydroxylase.

- 6315 ENHANCED REPRESENTATION OF HL-A ANTIGENS ON HUMAN LYMPHOCYTES AFTER MITOGENESIS INDUCED BY PHYTOHEMAGGLUTININ OR EPSTEIN-BARR VIRUS. (Eng.) McCune, J. M. (Biological Lab., Harvard Univ., Cambridge, Mass. 02138); Humphreys, R. E.; Yocum, R. R.; Strominger, J. L. *Proc. Natl. Acad. Sci. USA* 72(8):3206-3209; 1975.

Qualitative and quantitative alterations of HL-A antigens were studied during transformation of normal peripheral blood lymphocytes (PBL) with phytohemagglutinin (PHA) or Epstein-Barr virus (EBV). Cell types used in the study were derived from one individual (RH). PBL were prepared by Ficoll-Hypaque, density gradient centrifugation; phytohemagglutinin-stimulated lymphocytes (PHAL) were generated by culture of PBL with PHA for variable periods of time and PHA concentration; a lymphoblast B-cell line (RH-1) was established by transformation of PBL with Epstein-Barr virus. The amounts of HL-A antigens present on cells of the various types were determined by quantitative absorption assays. The RH-derived cells were histotyped to be HL-A3, W-28, HL-A7, and HL-A27, and corresponding alloantisera were used for the absorp-

tion assays. The cell surface areas of PBL, PHAL, and RH-1 were determined by average surface areas calculated from 2 diameter measurements in a phase contrast microscope. Relative cell surface areas were also determined, based on determinations of radioiodinatable surface proteins or of 5'-nucleotidase activity. The results showed that the amount of HL-A antigens present on PBL was increased about 11-fold after stimulation with PHA and about 36-fold after transformation with Epstein-Barr virus. This increase applied to all four HL-A specificities. The response to PHA was dependent on dose. Ratios of surface areas of PBL/PHAL/RH-1 were 1.0/1.9/3.2 by geometry, 1.0/2.3/(not determined) by radioiodine incorporation, and 1.0/1.5/2.5 by 5'-nucleotidase activity. These area measurements show that the increased expression of HL-A antigens on PHAL and RH-1 is not accompanied by a similar large increase in cell surface area. It thus appears that, whatever the mechanism, lymphocytes with widely different representations of HL-A can be obtained. It is suggested that if HL-A antigens are mediators of intercellular recognition, an increased density of HL-A antigens may imply heightened potential for contact with other cells or soluble factors.

- 6316 CONTROL OF GRANULOPOIESIS IN MAN: III. INHIBITION OF COLONY FORMATION BY DENSE LEUKOCYTES. (Eng.) Baker, F. L. (Dept. Medicine, Queen's Univ., Kingston, Ontario, Canada); Broxmeyer, H. E.; Galbraith, P. R. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):337-342; 1975.

Suspensions of bone marrow cells isolated from normal individuals will grow in agar medium to form colonies, provided that they are underlayered by a feeder layer containing WBC. When the more dense cells (mainly granulocytes) are removed by a centrifugal operation prior to preparation of the feeder layer, the residual leukocyte cells are able to stimulate colony-formation by the bone marrow cells to a much greater extent. Adding back the denser cells to restore the original composition of the feeder layer reduces the colony-stimulating activity of the layer to its initial level. The addition of surplus dense cells does not depress the activity further. It appears that granulocytes are able in some way to exert an inhibitory effect on the formation of colonies by bone-marrow cells.

- 6317 THE MACROPHAGE CONTENT OF SOME HUMAN TUMOURS. (Eng.) Gauci, C. L. (Chester Beatty Res. Inst., Clifton Ave., Belmont, Sutton, Surrey, SM2 5PX U.K.); Alexander*, P. *Cancer Lett.* 1(1):29-32; 1975.

The number of macrophages present in 44 surgically removed breast tumors and melanomas was determined by making a cell suspension and measuring the proportion of cells that bound a heterologous anti-macrophage serum and spread rapidly in culture. The macrophage content of the different tumors ranged from 0-30%. The malignant tumors that were known to have metastasized, as well as metastatic lesions, all contained less than 10% macrophages, whereas cancers for which there was no evidence of spread at opera-

tion had widely varying numbers of macrophages. All benign breast lesions had a low content of macrophages, and four tumors having the highest numbers of macrophages showed inflammatory changes on histological examination. A possible interpretation is that the cells giving rise to the benign lesions are not antigenic.

6318 LOCALIZATION OF NEUROBLASTOMA *IN VIVO* WITH TUMOR-SPECIFIC ANTIBODIES. (Eng.)

Terman, D. S. (Dept. of Medicine, Univ. of Colorado, Denver, Colo. 80220); Stewart, I.; Travel, A.; Kirch, D. *Cancer Res.* 37(7):1761-1766; 1975.

Studies of the mouse C-1300 neuroblastoma were undertaken to isolate tumor-specific antibodies and harness them for detection of tumors *in vivo*. Preliminary investigations demonstrated the strain-growth specificity of the neuroblastoma in A/Jax male mice and established the requirement for tumor viability for successful adoptive passage. Id passaged tumor permitted extended survival of mice so that serum could be sampled at intervals for the presence of tumor-specific antibodies. By means of an indirect radioimmunoassay with glutaraldehyde-fixed tumor cells as antigen, tumor-specific antibodies were identified in the serum of tumor-bearing host six days after inoculation, with a steady increase in antibody levels observed through day 22. An eluate in which immunoglobulin G antibodies were identified by immunoelectrophoresis was obtained from purified tumor cells by acid buffer incubation. These antibodies were labeled with ^{125}I , absorbed with normal tissues, and injected into tumor-bearing mice. A selectively collimated, single-probe isotope localization was positioned over the id tumor, while the rest of the animal was shielded with lead. With this device, ^{125}I -neuroblastoma eluate was significantly taken up in the neuroblastoma but not in the mouse head or in a reticulum cell sarcoma control. Increasing uptake of MOPC 141 ^{125}I -immunoglobulin G was not observed in either tumor. These studies suggest that the mouse neuroblastoma may provide a source of tumor-specific antibodies and that, with sensitive monitoring devices, these antibodies may be utilized to localize occult neoplastic tissue *in vivo*.

6319 ANTIBODY TO A MOLECULARLY-DEFINED ANTIGEN CONFINED TO A TUMOUR CELL SURFACE. (Eng.)

Stevenson, G. T. (Tenovus Res. Lab., General Hosp., Southampton SO9 4XY, England); Stevenson, F. K. *Nature* 254(5502):714-716; 1975.

Definable idiotypic determinants were demonstrated on the surface immunoglobulin (Ig) of neoplastic B lymphocytes of leukemic guinea pigs and anti-V (amino acid sequence in the variable regions of Ig molecules) was raised to demonstrate tumor-specific antigens. The L₂C leukemia of strain 2 guinea pigs maintained by repeated passage *in vivo* demonstrated IgM on the surface of large B lymphocytes. Approximately 100,000 molecules/cell were shed with a half life of five hours. Limited proteolysis of cells

with papain cleaved the surface IgM *in situ* and released Fab₂ fragments, bearing V regions, into the supernatant. Antibody to the V regions was raised by injecting washed Fab₂-laden immunosorbent from 3×10^{10} cells directly into two sheep and serum was obtained 1-3 wk after a second antigen injection. Unwanted antibody activities (to the Fab₂ C region and to normal guinea pig cell surfaces) were removed by passaging IgG from the sera through normal strain 2 guinea pigs. The antibody serum was tested for reactivity against L₂C cells and syngeneic normal lymphocytes by immunofluorescence and migration inhibition. A positive staining reaction and inhibition of migration were observed only with antibody serum and L₂C cells. Molecular discrimination of the capping-pinocytosis phenomenon confirmed that the tumor-specific antibody was directed against cell surface Ig. The authors suggest that the availability of antisera to a tumor specific molecule, which can be identified and quantified, and which appears in the cellular environs as a result of turnover at the cell surface, is of considerable research and therapeutic value.

6320 NON-ORGAN-SPECIFIC AND TUMOUR-SPECIFIC ANTIBODIES IN CHILDREN WITH WILMS' TUMOUR.

Kumar, S. (Medical Sch., Univ. Manchester, Manchester, England); Taylor, G. *Int. J. Cancer* 16:448-455; 1975.

Immunofluorescence (IF) and absorption procedures were used to determine whether tumor-specific antibodies could be detected in children with Wilms' tumor. Samples of sera were obtained from 45 children with Wilms' tumor, 27 with solid tumors of non-renal origin, and 52 from control children with minor surgical conditions. The target cells which were used were obtained from cell cultures of Wilms' tumor, of "normal kidney" from Wilms' patients, and of normal human kidneys. Substrates for IF studies, in the form of fixed tissue-culture cells, were incubated first with test sera, then with fluorescent anti-Ig sera. For the absorption studies, those sera which gave positive IF were first absorbed with tissue-cultured human skin fibroblasts. Sera which remained positive for IF after such absorption were further doubly absorbed with pooled tissue-cultured normal human kidney cells. Of the sera from children with Wilms' tumor, 93.3% reacted with Wilms' tumor target cells, 91.1% with normal kidney cells from Wilms' patients, and 71.1% with normal kidney cells. Of sera from children with non-renal tumors, 70.4% reacted with Wilms' tumor cells, 29.6% with normal kidney cells from Wilms' patients, and 55.5% with normal kidney cells. Of sera from control children, 17.3% reacted with Wilms' tumor cells, 5.8% with normal kidney cells from Wilms' patients, and 11.5% with normal kidney cells. Results of the absorption tests and various control IF tests showed that the reactive antibody present in a high proportion of sera from both the Wilms' tumor and non-renal tumor groups was non-organ-specific auto-antibodies. Thus, only 3/45 sera in the Wilms' group and 1/27 of the non-renal tumor group contained antibody reacting with normal kidney cells. Further, only 1/45 sera in the Wilms' group contained tumor-specific antibody. It was speculated that the non-organ-specific anti-

bodies arose as a result of liberation of non-organ-specific antigens from the tumor, that they were due to an adjuvant-like property derived from the tumor, or that they preceded the tumor and indicated an abnormal immune state predisposing to tumor formation.

6321 TUMOUR-ASSOCIATED TRANSPLANTATION ANTIGEN
IN SERA OF RATS WITH LARGE RSV-INDUCED

SARCOMAS. (Eng.) El Ridi, R. (Inst. Experimental Biology and Genetics, Czechoslovak Acad. Sciences, Flemingovo nam. 2, Prague 6, Czechoslovakia); Bubenik, H. *Int. J. Cancer* 16(1):83-90; 1975.

A factor inhibiting tumor growth in syngeneic hosts was found in the sera of inbred Lewis rats carrying Rous sarcoma virus-induced tumour (RSL). The findings presented here suggest that the serum factor is a tumor-associated transplantation antigen (TATA) shed from the neoplasm into the circulation. All the tumor-bearers' sera tested with RSL cells were negative in indirect membrane immunofluorescence; however, on passive transfer into syngeneic rats, the sera (0.2 ml, sc) protected the animals against the growth of an RSL tumor inoculum (10^3 cells, sc). A similar protective effect was also observed after injection of TATA prepared from RSL cell membranes by solubilization with potassium cholate. When incorporated into Freund's adjuvant, tumor-bearers' sera immunized the animals against a subsequent RSL sarcoma graft. Sera collected from immunosuppressed rats bearing large sarcomas, which presumably contain neither tumor-specific antibody nor antigen-antibody complexes, transferred inhibition of tumor growth to syngeneic hosts. Intact immunological reactivity of recipients was a necessary prerequisite for the protective effect of sera, since the passive transfer of an inhibitory serum to immunosuppressed rats did not inhibit tumor growth. It is assumed that the TATA present in tumor-bearers' serum is released from the growing neoplasm as a result of either cell death or membrane metabolic turnover.

6322 THE RELATIONSHIP BETWEEN NASOPHARYNGEAL
CARCINOMA AND THE HL-A SYSTEM AMONG TUNI-

SIANS. (Eng.) Betuel, H. (Cent de Transfusion Sanguine de Lyon, Beynost, 01700 Miribel, France); Camoun, M.; Colombani, J.; Day, N. E.; Ellouz, R.; de-The, G. *Int. J. Cancer* 16(2):249-254; 1975.

A study was conducted to determine whether or not a similar relation of HL-A antigens and increased risk of nasopharyngeal carcinoma (NPC) found among the Chinese (Singapore, 1975) is also present in Tunisians. Blood samples were obtained from 109 NPC patients, in 39 patients with other forms of cancer, and in 45 intermittent noncancerous controls. More than two monospecific antisera were used to detect each HL-A antigen. No significant differences were observed between the NPC and nonNPC patients for any specific antigen; however, there was a slightly higher frequency of A2 among the nonNPC cases than among the NPC cases. At the first HL-A locus, no association was found between A2 and NPC, in contrast to the Singapore results. Thus, the results were similar to those found in Singapore, but the effect

was less marked and not statistically significant. The authors conclude that although the results are close to what might be expected for an association of increased NPC risk and the second locus blank, the study would have to be continued for several years to give statistically significant results.

6323 MEASUREMENT OF CARCINOEMBRYONIC ANTIGEN
IN SERUM OF PATIENTS BY USING A TECHNIQUE
OF PASSIVE HEMAGGLUTINATION INHIBITION. (Eng.)

Anthony, R. L. (Univ. Maryland Sch. Medicine, Baltimore, Md. 21201); Sosnowski, K. M. *Clin. Immunol. Immunopathol.* 4(3):362-373; 1975.

A passive hemagglutination inhibition (PHI) test was developed for routine clinical detection of nanogram quantities of carcinoembryonic antigen (CEA) in microliter volumes of untreated serum. This was accomplished by sensitizing O-negative human RBC with purified CEA derived from a pool of human primary adenocarcinomas of the colon and rectum. The purification procedure for perchloric acid-extracted CEA included elution from Sepharose 4B and Sephadex G-200 columns. The sensitization was carried out using the bisdiazotized benzidine technique. Sera from patients were examined for their capacity to inhibit the agglutination of the sensitized RBC in the presence of a predetermined amount of goat anti-CEA serum. The anti-CEA serum was prepared by hyperimmunization of goats with the purified CEA and absorption of the anti-serum with perchloric acid extracts of normal colons and packed human AB-positive RBC. Positive sera were defined as those which produced inhibition of agglutination at a dilution of 1:8 or greater under the conditions of the test. The level of 1:8 was based on the finding that 32 out of 36 normal sera failed to inhibit at dilutions of 1:8. The percentage of positive sera was 82 for primary adenocarcinomas, 55 for all other cancers, 62 for benign diseases of the gastrointestinal tract, 60 for alcoholic cirrhosis, and 17 for normal healthy controls. Long-term follow up studies were recommended for detection of increased levels of CEA in progressive disease. Of 108 sera which were positive by a radioimmunoassay (RIA), 92 exhibited positive results by the PHI-assay. The advantages of the PHI assay over the RIA procedure include a requirement for only 25 μ l of untreated serum, a time of completion of the test of only 18 hr, and greater simplicity.

6324 CARBOXYL ESTERASE ACTIVITY OF CARCINOEM-
BRYONIC ANTIGEN? (Eng.) Thomas, P.

(Royal Marsden Hosp., Fulham Road, London SW3 6JB England); Westwood, J. H. *Br. J. Cancer* 32(3):401-402; 1975.

A kinetic investigation of carboxylesterase activity in six purified carcinoembryonic antigen (CEA) preparations indicates, contrary to previous reports, that no carboxylesterase or N-acetyl-glucosaminidase activity was present. Three of the CEA samples were from liver metastases of human colorectal carcinoma. Esterase activity was assayed at the University of Lausanne. Esterase activity was assayed

using p-nitrophenyl acetate, α -naphthyl acetate and β -naphthyl acetate as substrates. In no case did CEA or oxidized CEA (performic acid) cause significant hydrolysis of these substrates. None of the CEA samples hydrolyzed p-nitrophenyl 2-acetamido-2-deoxy- β -D-glucopyranoside, contrary to a previous report.

- 6325 PURIFICATION OF SOLUBLE COMPLEMENT-FIXING ANTIGENS FROM TWO BURKITT'S LYMPHOMA CELL LINES: CONDITIONS AFFECTING THE STABILITY AND RECOVERY OF ANTIGENS AND ANTIBODIES. (Eng.) Weliky, N. (Systems Group of TRW Incorporated, R1/2094, One Space Park, Redondo Beach, Calif. 90278); Leaman, D. H., Jr.; Kallman, B. J. *Immunology* 29(4):779-790; 1975.

To improve the reliability of immunological tests for tumor antigens, an effort was made to purify such antigens as a prelude to preparation of tumor-specific antibody. The source of the antigen in this study was lysates of P3HR-1 and Raji cell lines. Starting material was prepared by freeze-thawing of cells, followed by sonication, centrifugation at 44,000 g, and discarding of the pellet. Complement fixation (CF) was used as the assay. Two Epstein Barr virus (EBV)-associated, fluorescent-labeled antibody (FA), CF-positive human sera and one FA, CF-negative human serum were used for preparation of immunoadsorbents. In separate experiments, the antigens were purified to varying degrees by immunoabsorption, $(\text{NH}_4)_2\text{SO}_4$ precipitation, or polyacrylamide gel electrophoresis. Conjugates of EBV-FA-positive, CF-positive human serum with cyanogen bromide-activated Sephadex G-200 extracted the antigen from the extracts. The antigens could then be recovered upon dissociation with glycine-HCl at pH 2-2.3, with glycine-NaOH at pH 12 or with 5.5 M potassium iodide. Recoveries were relatively low. Yields were negligible, however, if the immunoadsorbent was prewashed at pH 2.3 or 12 before the absorption step. This was because of instability of the antigen-specific antibody attached to the immunoadsorbent. The antigen was not appreciably absorbed by Sephadex G-200 which had been conjugated with CF-negative serum. The antigen was inactivated at pH 2.3 and was irreversibly bound to Sephadex G-200 conjugates which had not been exposed to large excesses of serum. Purification by immunoabsorption was indicated by reduction in protein concentration in the eluates and by the occurrence of fewer bands on gel electrophoresis. The soluble P3HR-1 antigen was precipitated by one third saturated $(\text{NH}_4)_2\text{SO}_4$ or by 0.05 M glycine at pH 4.0. The Raji antigen was similarly precipitated by $(\text{NH}_4)_2\text{SO}_4$. The $(\text{NH}_4)_2\text{SO}_4$ purified P3HR-1 antigen lost activity after 5 days at 6 or -80 C, while the corresponding purified Raji antigen was stable under the same conditions. Polyacrylamide gel electrophoresis of Raji soluble antigen revealed activity only in the upper 20% of the gel. The number of bands in the upper half of polyacrylamide gels, after electrophoresis of immunoadsorbent of $(\text{NH}_4)_2\text{SO}_4$ purified antigen preparations was small. It appeared that elution of antigen from the upper section should

result in considerable further purification. It was concluded that purification conditions were limited by the instability of both antigen and antibody activity.

- 6326 INHIBITION OF *IN VITRO* LYMPHOPROLIFERATIVE RESPONSES TO TUMOR-ASSOCIATED ANTIGENS BY SUPPRESSOR CELLS FROM RATS BEARING PROGRESSIVELY GROWING GROSS LEUKEMIA (Eng.) Glaser, M. (Lab. of Immunodiagnosis, Natl. Cancer Inst., Building 8, Room 118, Bethesda, Md. 20014); Kirchner, H.; Herberman, R. B. *Int. J. Cancer* 16(3):384-393; 1975.

Male W/Fu rats (8-10-wk-old) were injected sc with 1×10^8 or 1×10^9 Gross leukemia virus-induced rat lymphoma (C58NT)D cells in order to study the suppression of cellular immunity seen during progressive tumor growth. Rats injected with 1×10^8 cells (regressors) showed transient tumor growth followed by regression within two weeks. Rats injected with 1×10^9 cells (progressors) developed progressively growing tumors resulting in death in 30-40 days. Mixed lymphocyte tumor cell interaction (MLTI) was apparent in spleens of regressors 20-40 days after (C58NT)D injection, whereas no MLTI was demonstrable in spleens of progressors. Spleen cells from progressors also developed significant depression of mitogen reactivity as measured by stimulation of ^3H -thymidine uptake induced by phytohemagglutinin A (PHA) and concanavalin A (Con A). Spleen cells of regressors showed normal mitogen reactivity at all times. MLTI and mitogen reactivity of progressor spleen cells was restored by passing the cells through rayon adherence columns and by an iron/magnet technique. No MLTI of normal spleen cells was seen following these procedures. Spleen cells of progressors inhibited MLTI and mitogen reactivity of regressor cells when mixed at concentrations as low as 15%. The suppressive effect of progressor cells was eliminated by passage of the cells through rayon adherence columns or by treatment with the iron/magnet technique. Serum from progressor animals inhibited the MLTI and mitogen reactivity of regressor spleen cells. The results indicate that suppressor cells occur in spleens of animals with progressively growing tumors. These suppressor cells induce a humoral mediation of inhibition of both specific (MLTI) and nonspecific (PHA and Con A) cellular reactivity.

- 6327 HUMAN LUNG TUMOR ANTIGENS. (Eng.) McIntire, K. R. (Natl. Cancer Inst., Bethesda, Md.) Sizaret, P. P. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 295-307.

Two different soluble antigens were found associated with human lung tumors. Human Lung Tumor Antigen-1 (HLTA-1) was found in 8 of 10 lung tumors of 5 histological types: it was not found in extracts of either normal lung, fetal lung, or of 9 other neoplasms. It was, however, located in extracts of

normal esophagus and trachea. HLTA-1 possessed β -electrophoretic mobility, was not soluble in perchloric acid, and was destroyed by heating at 55° for 2 min. The second antigen (HLTA-2) was found in 7 of 10 lung tumors of 5 histological types: it was not found in extracts of normal tissues, including lung, except for spleen. Extracts of most neoplasms were negative, but HLTA-2 was demonstrable in melanomas, lymphomas, and 3 sarcomas. HLTA-2 was soluble in 0.6M perchloric acid, and could be demonstrated to be also present in concentrated perchloric acid extracts of fetal lung. The two antigens were distinctly different and showed no cross-reactivity: they were shown to be different molecular species from certain other tumor-related antigens, i.e. α 2H globulin, fetal ferritin, α -fetoprotein, and carcinoembryonic antigen. Their appearance in tissues was independent of each other, but they were also located simultaneously in 5 of 10 lung tumors. Neither antigen has been found in the serum of patients with lung cancer. Although neither of the two antigens are completely specific for carcinoma of the lung, both are quantitatively increased in the disease. HLTA-2 may be an onco-fetal antigen.

6328 THE HL-A AND ABO ANTIGENS IN TROPHOBLASTIC DISEASE. (Eng.) Mittal, K. K. (Northwestern Univ. Medical Sch., 303 East Chicago Ave., Chicago, Ill. 60611); Kachru, R. B.; Brewer, J. I. *Tissue Antigens* 6(2):57-69; 1975.

To test whether the fact that trophoblastic neoplasia contains paternal factors implicates a role for HL-A antigens in the incidence of the disease, patients with trophoblastic disease were studied with respect to possible deviations in phenotype frequencies of different HL-A antigens or deviations in HL-A incompatibilities in male spouses of the patients. Tests were also made for deviation in incidence of different male-female combinations of ABO blood groups and for the presence of cytotoxic antibody in patient sera toward lymphocytes of normal persons or of other patients with the same disease. The HL-A and the ABO antigens were investigated in three trophoblastic diseases: hydatidiform mole, invasive mole and choriocarcinoma. No statistically significant deviations in phenotype frequencies of 25 different HL-A antigens or the ABO antigens were seen when 111 Caucasian patients were compared with 1,259 healthy Caucasian controls. However, an increase in the incidence of HL-A11 antigen was found in 39 patients who currently had the disease, but not in 72 who had recovered from such disease. Further, an increase in the frequency of W18 antigen was observed among 18 patients who currently had invasive disease (choriocarcinoma or invasive mole), but not in 44 who had recovered from such disease. If valid for larger patient populations, these increases may suggest association of HL-A11 and W18 antigens with the "morbidity" of the disease. No increase in histocompatibility was seen in 45 patient-couples over 67 control-couples in terms of decrease in the number of male spouse's HL-A incompatibilities, and no significant difference was observed in the incidence of different male-female combinations of ABO blood groups between 95 patient-couples and an equal num-

ber of control couples. Lymphocytotoxic antibodies were found in the sera of 64/178 patients examined; HL-A specific antibodies were found in 30/178. Of these, 30, 24 had molar pregnancies and six had choriocarcinoma. Whether these antibodies have a role in the destruction of neoplastic tissue remains to be determined.

6329 CELL SURFACE ANTIGEN EXPRESSION ON CHEMICALLY INDUCED MURINE LEUKAEMIAS. (Eng.)

Birch, J. M. (Paterson Lab., Manchester M20 9BX, England); Moore, M.; Craig, A. W. *Br. J. Cancer* 31(6):630-640; 1975.

The immunogenicity of murine leukemias induced by chemical carcinogens or irradiation in C57Bl or (C57Bl x DBA2) F1 hybrid mice was studied *in vivo* by transplantation and *in vitro* by indirect membrane immunofluorescence (IF) using syngeneic immune or allogeneic immune antisera. Two of five leukemias tested for immunogenicity by assessment of the capacity of syngeneic mice specifically immunized with irradiated (3 Krad) cells to reject small challenge inocula (10^3 - 10^4 cells) displayed weak neoantigenicity while three were non-immunogenic by criterion. Antibodies directed against cell-surface antigens of the immunizing cells of seven leukemias were not detectable by immunofluorescence tests using sera from the respective immunized mice. H-2 histocompatibility antigens readily identified on normal lymphoid cells using reference Balb/c anti-C57Bl (H-2^d anti-H-2^b) alloantisera could neither be detected on the majority of transplanted leukemias nor on nine primary leukemias in C57Bl mice induced by N-butyl-N-nitrosourea (BNU). Two of the transplanted leukemias showed greatly diminished capacity for absorption of alloantibody compared with normal spleen cells. Transplantation to H-2 different recipients, in which the leukemic cells were invariably rejected, generated a strong humoral antibody response, which was demonstrable against normal lymphoid cells. Failure to demonstrate significant antibody binding by indirect immunofluorescence tests with immune sera, or by absorption, is presented as evidence that H-2 antigen expression is substantially modified on BNU-induced leukemia cells. These findings have implications for the detection of tumor neoantigens on chemically induced leukemias.

6330 SOLUBLE TUMOR REJECTION ANTIGENS FROM MEMBRANES OF VIRALLY TRANSFORMED NEOPLASTIC CELLS. (Eng.) Law, L. W. (Natl. Cancer Inst., Bethesda, Md.); Appella, E.; Chang, K. S. S.; Henriksen, O. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 228-231.

Tumor-specific transplantation antigens (TSTA, associated with neoplastic cells having tumor rejection capacities) were extracted and solubilized from two types of neoplasms by limited papain digestion followed by Sephadex column fractionation. The DNA-containing oncogenic virus mKSA, a simian

virus 40 (SV40)-transformed neoplasm of BALB/c mice, and an RNA-containing oncogenic virus, RBL-5, a lymphoblastic leukemia induced in a C57Bl/6 mouse served as sources of TSTA. Crude membrane (CM) prepared from mKSA-ASC (ascites form) afforded complete protection against a challenge of 10^4 - 10^5 neoplastic cells and partial protection against 10^6 cells. Crude soluble material (CS) afforded complete protection against 10^4 cells and partial protection at 10^5 cells. CM preparations from both ASC and TC (tissue monolayer culture) cell lines were equally immunogenic. The immunogenic activity was contained mainly in the peak (F2 fraction) that was positive for alloantigenic (H-2) activity. This specific TSTA activity was titrated *in vivo* to as low as 5 μ g protein/mouse, representing an immunogen yield of approximately 20% for the CS preparation. Despite the strong immunogenicity observed in these tumor rejection studies, anti-mKSA serum was not cytotoxic for any of the SV40 target cells nor was any effective anti-serum produced by CM or CS. Following immunization with CM, CS, and the F2 fraction of TSTA prepared from RBL-5, significant inhibition of growth was observed for LSTRA, a MLV-induced leukemia and BL-3, a FLV-induced leukemia. In contrast to immunogenic preparations of mKSA, both CM and CS of RBL-5 membranes induced cytotoxic antisera in syngeneic mice and inhibition of complement dependent cytotoxicity. In the F2 pooled fraction and the CM preparation, H-2 specificities 2 and 28 were also detected. Specific immunogenicity was retained again in the F2 peak containing alloantigen activity. In a micro-complement fixation assay, cytotoxic antisera detected a specific component that is not related to structural viral proteins. Thus, the solubilized antigen of RBL-5 appears to be a new cellular antigen analogous to the TSTA of a DNA-oncogenic virus-induced neoplasm.

6331 LIVER DIFFERENTIATION AND THE ESTROGEN-BINDING PROPERTIES OF α -FETOPROTEIN.

(Eng.) Uriel, J. (Institut de Recherches Scientifiques sur le Cancer, Villejuif, France); Aussel, C.; Bouillon, D.; Loisillier, F.; de Nechaud, B. *Ann. N.Y. Acad. Sci.* 259:119-130; 1975.

Attempts were made to explain differences in estradiol-binding capacity of human serum and of sera of rats or mice, where the binding capacity is taken as a measure of α -fetoprotein (AFP) concentration. Less than 0.2% of the total AFP present in human serum binds estradiol, while 20-30% of that in rat serum and 90% of that in rat amniotic fluid binds the estrogen. These findings suggest the possibility that AFP occurs in two different conformational states and, therefore, that differences in estrogen-binding capacities may be explained by changes in the proportion of the two molecular variants. Using an *in vitro* radioautographic method of cell-affinity labeling with tritiated estrogens, it was found that the localization of radioactivity was preferentially cytoplasmic, occasionally in the cytoplasmic or nuclear membranes, most frequently in intermediate patterns. In rat embryos beyond 14 days of gestation, radiolabeled cells were observed only in the liver and

gastrointestinal tract. Three weeks after birth, the labeling was limited mostly to the spleen. Radiolabeled cells reappeared in the liver of rats bearing primary hepatic tumors. The cells were usually localized among neoplastic trabeculae and at the proximity of portal areas of hepatocellular carcinomas as well as inside the duct-like structures of cholangiocarcinomas. In the rat and human hepatocarcinomas, the morphology of the labeled elements seemed related to that of the "transitional" cells, which were small round or oval cells with an elongated or kidney-shaped nucleus. The expected correlation between serum AFP and number of labeled cells was not confirmed in all cases, however. As an explanation, it was speculated that the "transitional" cells are intermediate phenotypes from "oval" cells to mature hepatocytes or cholangiocyte cells. According to the hypothesis, only these "transitional" cells are AFP producers. This hypothesis explains the discrepancies found between serum AFP levels and the number of radiolabeled cells.

6332 FETAL PATHOPHYSIOLOGY OF HUMAN α -FETO-PROTEIN. (Eng.) Seppala, M. (University Central Hosp., Helsinki, Finland). *Ann. NY Acad. Sci.* 259:59-73; 1975.

α -Fetoprotein (AFP) levels in more than 2,800 samples from fetal and maternal sera and amniotic fluid were analyzed by radioimmunoassay. On the basis of the results, an account is given on the pathophysiology of AFP in human gestation. The levels in fetal and maternal sera showed a trend toward higher concentrations in Rh-immunized and diabetic pregnancies and lower concentrations in toxemic pregnancies when comparisons were made with levels in normal pregnancies. This phenomenon was suggested to reflect differences in the biological maturation timetable of the fetal liver under these conditions. For any given week of gestation, fetal and maternal AFP levels showed a positive correlation, and larger placentas were associated with higher maternal AFP levels than were smaller placentas. In normal gestation the peak maternal AFP levels occurred during the mid-third trimester, and the level decreased towards term. Maternal AFP levels which were high for given dates were often associated with intrauterine fetal death or with severely abnormal fetal development, whereas fetal levels did not show striking deviations from normal under similar conditions. Abnormal elevation of maternal AFP was likely to result from increased fetomaternal transfusion and/or resorption by the mother of fetal elements. Conditions in which the maternal AFP assay was most likely to improve the clinical diagnosis included threatened abortion, placental abortion, and perhaps some neural tube malformations. AFP in the amniotic fluid was of fetal origin and, like fetal AFP, amniotic AFP levels were highest at the 14th wk of gestation and decreased thereafter. Amniotic levels, however, were 200-300 times lower than fetal levels. The significant correlation of decreasing AFP levels with advancing gestation made AFP a useful marker in the assessment of gestational age; high levels, however, could not be used to indicate prematurity. Raised amniotic AFP levels were found in anencephaly, meningocele,

hydrocephalus, esophageal atresia, tetralogy of Fallot, intrauterine fetal death, congenital nephrosis, and severe Rh-hemolytic disease. Antenatal diagnosis of severely disabling fetal defects such as anencephaly and spina bifida is now acceptable based on AFP estimation in conjunction with sonar examination. As for other malformations, data from early pregnancy are insufficient or totally lacking, but the finding of a variety of conditions with raised amniotic AFP during the third trimester should encourage prospective studies aimed at extending this knowledge.

6333 FACTOR SUPPRESSING α -FOETOPROTEIN PRODUCTION IN NEWBORN MICE. (Eng.) Tumyan, B. G. (Inst.: Experimental and Clinical Oncology AMS USSR, Moscow 115478 U.S.S.R.); Svet-Moldavsky, G. G.; Karmanova, N. V. *Nature* 255(5505):244-245; 1975.

The nature of the factor which suppresses α -feto-protein (AFP) production in embryonic liver cells of BALB/c mice after the termination of the embryonic period was investigated. Families of newborn mice were divided into two groups: One group was untreated and the other group received daily injections of serum or extracts of various organs of syngeneic adult mice and embryo. The volume of the injections increased as the animals aged. Each mouse killed on day 10 had received 2.1 ml 20% extract. Factors suppressing AFP production were found in the serum, small and large intestine, liver, lung, brain, thymus, spleen, and kidneys of adult mice. The factor was hardly detectable in the small intestine of mice embryos, in the whole embryo, or in striated muscles of adult mice. Heating of the small intestine extract of 60 C for 45 min inactivated the suppression mechanism, suggesting the protein nature of the factor. Whether this factor acts by suppressing AFP syntheses in embryonic cells or by inhibiting multiplication of the AFP-producing cells has yet to be determined.

6334 α -FETOPROTEIN AND HEPATITIS B ANTIGEN IN HEPATOCARCINOGENESIS. (Eng.) Sakurai, M. (Osaka Univ. Medical Sch., Osaka, Japan); Miyaji, T. *Ann. NY Acad. Sci.* 259:156-167; 1975.

Blood from 394 unselected autopsy cases was examined for hepatitis B antigen (HB Ag), hepatitis B antibody (HB Ab), and α -fetoprotein (AFP) in order to correlate an impaired cell-mediated immunity with hepatocarcinogenesis. Liver morphology of 71 cases of cirrhosis with hepatoma and 32 cases of cirrhosis without hepatoma was studied in detail by light microscopy and correlated to HB Ag, HB Ab, and AFP. The micro-Ouchterlony method, the single radial immunodiffusion method, the direct latex method and the radioimmunoassay method were used for AFP assay; the immune adherence hemagglutination method was used for HB Ag, and the passive hemagglutination method was used for HB Ab determinations. The immunofluorescent antibody technique was applied in frozen sections

to demonstrate localization of AFP and HB Ag in liver tissue in selected cases. Significantly lowered humoral immunity to HB Ag exposure was established for the cirrhosis with hepatoma cases. The exposure rate for both cirrhosis cases with hepatoma and cirrhosis cases without hepatoma was the same (48%), but about 80% of each exposed group were either HB Ag- or HB Ab-positive. The cirrhosis with hepatoma group tended to be HB Ag-positive, and the cirrhosis without hepatoma group tended to be HB Ab-positive. The lowered immune response seems to be specific to the hepatoma association, because the group with neoplasms other than the hepatoma reacted exactly the same as the group with the cirrhosis without hepatoma. Twenty-five percent of the cirrhosis with hepatoma were associated with inactive cirrhosis, and 75% were associated with active cirrhosis. Seventy-two percent of the inactive cirrhosis cases with hepatoma were exposed to HB Ag, but only 42% of the active cirrhosis cases with hepatoma were exposed to HB Ag. On the morphological basis, the inactive cirrhosis was interpreted as an impaired cellular immunity, and the active cirrhosis as a delayed hypersensitivity reaction. The possibility was discussed that both are important factors in the development of hepatoma preceded by cirrhosis. AFP tends to be positive in the inactive cirrhosis with hepatoma as well as HB Ag, but the relationship between AFP and HB Ag for hepatocarcinogenesis needs further investigation.

6335 IMMUNOLOGICAL ANALYSIS OF PLASMINOGEN ACTIVATORS FROM NORMAL AND TRANSFORMED HAMSTER CELLS: EVIDENCE THAT THE PLASMINOGEN ACTIVATORS PRODUCED BY SV40 VIRUS-TRANSFORMED HAMSTER EMBRYO CELLS AND NORMAL HAMSTER LUNG CELLS ARE ANTIGENICALLY IDENTICAL. (Eng.) Christman, J. K. (Mt. Sinai Sch. Medicine, New York, N.Y., 10021); Silverstein, S. C.; Acs, G. *J. Exp. Med.* 142(2):419-434; 1975.

The preparation and specificity of antibodies against the plasminogen activator produced by a line of simian virus 40 (SV40)-transformed hamster cells are described. Rabbits were inoculated sc with 2 ml plasminogen activator released by SV40 virus-transformed cells from hamster line HaK. The resulting antiplasminogen activator immunoglobulin (APA-IgG) inhibited the enzymatic activity of the plasminogen activator produced by SV40-transformed hamster cells, and the plasmin-catalyzed release of these cells from the tissue culture dish. APA-IgG was not cytotoxic for these cells even in the presence of complement, and did not inhibit their release of plasminogen activator. APA-IgG formed a single precipitin line in immunodiffusion plates using highly purified plasminogen activator as antigen. APA-IgG inhibited the plasminogen activator produced by newborn hamster lung cells and by an established diploid line (DON) of hamster lung cells, but did not inhibit plasminogen activators produced by normal or transformed hamster kidney cells or by cells of other species (mouse and human). These data suggest that (a) there are several immunologically distinguishable forms (isozymes) of plasminogen activators in

normal hamster tissues; (b) the plasminogen activators produced by normal hamster lung cells and by SV40 virus-transformed hamster embryo cells share antigenic determinants and are presumably the same isozyme, and (c) the plasminogen activators produced by different hamster tumor cells do not share antigenic determinants and are presumably different isozymes.

- 6336 *IN VITRO* HUMAN REACTIVITY TO STAPHYLOCOCCAL PHAGE LYSATE. (Eng.) Dean, J. H. (Dept. Immunology, Litton Bionetics, Inc., Kensington, Md. 20795); Silva, J. S.; McCoy, J. L.; Chan, S. P.; Baker, J. J.; Leonard, C.; Herberman, R. B. *J. Immunol.* 115(4):1060-1064; 1975.

The cell-mediated reactivity of normal individuals to staphylococcal phage lysate (SPL) was tested *in vitro* in the lymphocyte stimulation (LS) and leukocyte migration inhibition (LMI) assays. There were 95% positive responses in LS (stimulation ratio ≥ 3 with $p < 0.01$) and 67% positive responses in LMI (migration index ≤ 0.80). Enriched subpopulations of T and B lymphocytes were prepared with rosette formation and density gradient centrifugation. SPL stimulated lymphoproliferative responses in both T and B cell subpopulations whereas phytohemagglutinin (PHA) stimulated only the T cell subpopulation. Cord blood leukocytes were tested in the LS assay and 41% gave positive responses to SPL, 81% to PHA, and 17% with SLO. SPL appears to be a useful reagent for the *in vitro* study of cell-mediated reactivity, and may provide somewhat different information from that obtained with other mitogens or antigens.

- 6337 FURTHER OBSERVATIONS OF Fc RECEPTORS IN HUMAN MALIGNANT TISSUE AND NORMAL LYMPHOID TISSUE. (Eng.) Tønder, O. (Broegelmann Res. Lab. Microbiol., Univ. Bergen, Norway); Humphrey, L. J.; Morse, P. A., Jr. *Cancer* 35(3):580-587; 1975.

Twenty human malignant solid tumors of various histologic types (melanoma, neurofibrosarcoma, leiomyosarcoma, and carcinoma) were tested for the presence of Fc receptor using cryostat sections or single cell suspensions of fresh tissue. SRBC sensitized by various amounts of rabbit IgG antibodies served as indicator cells (EA). All tumors possessed Fc receptor, but to varying degrees; eight reacted more strongly than normal spleen without any relation to histologic type. The tumors that gave the strongest reactions in sections also formed the highest percent of EA rosettes in suspensions, thus indicating surface localization of receptors. The reactions with spleen sections localized to the B cell and monocytic areas; the latter also showed high avidity in reactions with uncomplexed IgG. Rabbit antisera to tumors, spleen, and peripheral lymphocytes (polyvalent ALS) inhibited the reactions, while a T-cell-specific ALS did not. Absorptions of the antisera with lymphocytes or tissue sediments of spleen and tumors removed the inhibiting activity, but sediments of muscle and kidney only reduced the titers. Again, results

with spleen sections paralleled those obtained with tumor sections. Apparently, the tumor Fc receptor is very similar to the Fc receptors present in normal lymphoreticular tissues.

- 6338 γ -GLUTAMYLTRANSFERASE FROM AZO DYE INDUCED HEPATOMA AND FETAL RAT LIVER: SIMILARITIES IN THEIR KINETIC AND IMMUNOLOGICAL PROPERTIES. (Eng.) Taniguchi, N. (Hokkaido Univ. Sch. of Medicine, Sapporo, 060, Japan); Saito, K.; Takakuwa, E. *Biochim. Biophys. Acta* 391(2):265-271; 1975.

The kinetic and immunologic properties of γ -glutamyltransferase from fetal Donryu rat liver were compared with those of γ -glutamyltransferase from azo dye-induced hepatomas of Donryu rats. Mean enzyme activity was 10 U/mg protein in 20 adult rat livers, 100 U/mg protein in ten fetal rat livers, and 410 U/mg protein in 20 hepatomas. The enzymes from hepatoma and from fetal liver did not differ significantly in pH optimum, K_m value for L- γ -glutamyl *p*-nitroanilide, or K_i value for L-serine in the presence of borate. Both enzymes were slightly activated by divalent cations such as Mg^{2+} and Ca^{2+} , but not monovalent cations such as Na^+ or K^+ . Zinc ion was a potent inhibitor of the enzymes. The two enzymes showed no significant difference in stability when incubated at 58 C for 60 min in the presence of 0.02 M glutathione. Rabbit anti-sera against the purified hepatoma enzymes inhibited both this enzyme and the fetal liver enzyme by about 80%. The fetal liver enzyme also reacted with the hepatoma antisera in the precipitin reaction, and cross-reactivity was observed between the hepatoma and fetal liver enzyme. These findings indicate the γ -glutamyltransferase from fetal liver and that from hepatoma are structurally identical and consist of the same enzyme protein. The data also demonstrate that the ontogenic reversion of the enzyme did not involve alterations in gene expression.

- 6339 SELECTION FOR HIGH IMMUNOGENICITY IN DRUG-RESISTANT SUBLINES OF MURINE LYMPHOMAS DEMONSTRATED BY PLAQUE ASSAY. (Eng.) Fuji, H. (Roswell Park Mem. Inst., New York State Dep. Health, Buffalo); Mihich, E. *Cancer Res.* 35(4):946-952; 1975.

The immunogenicity of lymphoma L1210 and three L1210 sublines, resistant to methylglyoxal bis(guanyldrazone), 4,4'-diacetyldiphenylurea bis(guanyldrazone), or guanazole (L1210/GZL), respectively, was evaluated. Syngeneic DBA/2J mice were given a single ip injection of serially diluted suspension of irradiated cells from L1210 or L1210 sublines. Five days later, spleen cells from the immunized mice were tested for the presence of plaque-forming cells using the immunizing lymphoma cell lines as target. Sera collected from the animals were examined for cytolytic antibody activity by lysis in gel using the same target cells. For comparison, the H-2 immunogenicity of L1210 and its sublines was investigated in H-2 incompatible allogeneic mice. All sublines showed increased immunogenicity and susceptibility to lysis as compared to

L1210 cells. The number of plaque-forming cells per spleen ranged from 100 for L1210 to 4450 for L1210/GZL, the most immunogenic subline, and the antibody titer ranged from 1/8 for L1210 to 1/128 for L1210/GZL. All the sublines carried common tumor-associated antigens that apparently made primary contributions to the increased immunogenicity. The common tumor-associated antigens were also expressed on L1210 cells, although to a lesser degree, as evidenced by the definite, albeit low, capacity of L1210 cells to absorb DBA/2J anti-L1210/GZL antibodies. Spleen and thymus cells of DBA/2J mice as well as unrelated murine ascites tumor cells did not cause significant absorption of these antibodies. Only a partial inverse relationship could be demonstrated between tumor-associated antigens and H-2 immunogenicity. L1210/GZL showed the highest immunogenicity for tumor-associated antigens but the lowest for H-2. The results are compatible with the hypothesis that the increased immunogenicity of drug-resistant L1210 sublines is attributable to the selection of preexisting highly immunogenic cells during immunosuppression by treatments selecting for drug resistance.

6340 NATURAL CELL-MEDIATED CYTOTOXIC REACTIVITY WITH MOUSE LEUKEMIA CELLS [abstract]. (Eng.) Lavrin, D. H. (Litton Bionetics, Inc., Kensington, Md.); Nunn, M.; Herberman, R. B. *Proc. Am. Assoc. Cancer Res.* 16:148; 1975.

6341 CELL-MEDIATED IMMUNITY AGAINST ALLOGENEIC AND AUTOLOGOUS TUMOR CELL EXTRACTS IN BREAST CANCER PATIENTS [abstract]. (Eng.) Silva, J. S. (Med. Cent., Keesler Air Force Base, Miss. 39531); Leonard, C. M. *Proc. Am. Assoc. Cancer Res.* 16:148; 1975.

6342 SECONDARY CELL-MEDIATED CYTOTOXIC RESPONSE TO SYNGENEIC TUMORS [abstract]. Holden, H. T. (Natl. Cancer Inst., Bethesda, Md.); Shen, J. C.; Glaser, M.; Herberman, R. B. *Proc. Am. Assoc. Cancer Res.* 16:149; 1975.

6343 CELL-MEDIATED-IMMUNITY TO CHEMICAL CARCINOGENS. (Eng.) Thor, D. E. (Univ. Texas Health Sci. Cent. San Antonio); Sanford, B. A.; Reichert, D. F.; Flippen, J. H. *Fed. Proc.* 34(3): 990; 1975.

6344 SUPPRESSION OF CYTOTOXICITY BY IRA AND BY A PEPTIDE FRACTION FROM CANCER SERUM. (Eng.) Constantian, M. B. (Boston Univ. Med. Cent., Mass.); Nimberg, R. B.; Schmid, K.; Cooperband, S. R.; Mannick, J. A. *Fed. Proc.* 34(3):1024; 1975.

6345 EFFECT OF AGING ON CELL MEDIATED IMMUNITY (CMI) IN BALB/c MICE. (Eng.) Walters, C. S. (Univ. Colorado Med. Cent., Denver, CO); Claman, H. N. *Fed. Proc.* 34(3):987; 1975.

6346 CELL IMMUNITY INDICES IN PATIENTS WITH LUNG CANCER. (Rus.) Sokolova, I. I. (P. A. Herzen Res. Inst. Oncology, Moscow, U.S.S.R.); Pirogov, A. I.; Repina, F. F.; Erokhov, V. F. *Vopr. Onkol.* 21(7):32-36; 1975.

6347 THE IMMUNE RESPONSE TO ϕ X174 IN MAN. IV. PRIMARY AND SECONDARY ANTIBODY PRODUCTION IN PATIENTS WITH CHRONIC LYMPHATIC LEUKAEMIA. (Eng.) Hamblin, T. J. (Southmead Hospital, Bristol BS10 5NB, England); Jones, J. V.; Peacock, D. B. *Clin. Exp. Immunol.* 21(1):101-108; 1975.

6348 IMMUNE RESPONSE TO SPONTANEOUS RETICULUM CELL SARCOMA (RCS) IN SJL/J MICE [abstract]. (Eng.) Hescocx, M. (Sch. Med., Univ. California Los Angeles); Bonavida, B. *Proc. Am. Assoc. Cancer Res.* 16:162; 1975.

6349 IMMUNOLOGIC CHARACTERISTICS OF HODGKIN'S CELLS [abstract]. (Eng.) Kadin, M. E. (Univ. California, San Francisco, Calif.); Gold, S. B. *Proc. Am. Assoc. Cancer Res.* 16:156; 1975.

6350 EFFECT OF INFECTION WITH RADIATION LEUKEMIA VIRUS ON MURINE IMMUNE RESPONSES [abstract]. (Eng.) Lieberman, M. (Stanford Univ. Sch. Med., Calif.); Segal, S.; Kaplan, H. S. *Proc. Am. Assoc. Cancer Res.* 16:154; 1975.

6351 IMMUNOLOGICAL RELATIONSHIPS BETWEEN MUMTV, 734B AND A VIRUS-LIKE PARTICLE ISOLATED FROM HUMAN MILK [abstract]. (Eng.) McGrath, C. M. (Michigan Cancer Found., Detroit, Mich.); Furmanski, P.; Soule, H.; Grant, P.; Longley, C.; Rich, M. A. *Proc. Am. Assoc. Cancer Res.* 16:164; 1975.

6352 HEREDITARILY ATHYMIC-ASPLENIC MICE: A NEW MODEL FOR THE HETEROTRANSPLANTATION OF HUMAN MALIGNANCIES [abstract]. (Eng.) Lair, S. V. (Univ. Tennessee Memorial Res. Center, Knoxville, Tenn. 37920); Lozzio, B. B.; Lozzio, C. B.; Machado, E. A. *IRCS Med. Sci.* 3(10/Suppl.): 15; 1975.

6353 HISTOLOGY OF BRONCHIAL CARCINOMA AND REGIONAL LYMPH NODES--IMMUNOLOGICAL SIGNIFICANCE [abstract]. (Eng.) Di Paola, M. (Istituto Patologia Chirurgica II, Universita di roma, Rome, Italy); Bertolotti, A.; Colizza, S.; Coli, M. *IRCS Med. Sci.* 3(8):408; 1975.

6354 PATHOGENESIS OF NEURAL LESIONS IN MAREK'S DISEASE. I. ALLERGIC SKIN REACTION AGAINST MYELIN OF THE PERIPHERAL NERVES. (Ger.) Schmahl, W. (Institut fur Biologie, Abteilung Nuklearbiologie, D-8042 Neuherberg/Munchen, Ingolstadter Landstrasse, West Germany); Hoffmann-Fezer, G.; Hoffmann, R. *Z. Immunitaetsforsch.* 150(2):175-183; 1975.

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- 6356 HEMAGGLUTININS IN FRACTIONS OF HUMAN SARCOMAS [abstract]. (Eng.) Winters, W. D. (Univ. California Los Angeles Sch. Med.). *Proc. Am. Assoc. Cancer Res.* 16:147; 1975.
- 6357 SYNTHESIS AND TURNOVER OF INTRACISTERNAL A-PARTICLE STRUCTURAL PROTEIN IN CULTURED NEUROBLASTOMA CELLS. (Eng.) Lueders, K. K. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Kuff, E. L. *J. Biol. Chem.* 250(13):5192-5199; 1975.
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- 6361 ASSOCIATION OF AN ISOMERIC SPECIES OF CARCINOEMBRYONIC ANTIGEN WITH NEOPLASIA OF THE GASTROINTESTINAL TRACT. (Eng.) Edgington, T. S. (Scripps Clinic and Res. Foundation, 476 Prospect St., La Jolla, Calif. 92037); Astarita, R. W.; Plow, E. F. *N. Eng. J. Med.* 293(3):103-107; 1975.
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- 6367 A NEW MEMBRANE ANTIGEN ON HUMAN CULTURED CELLS [abstract]. (Eng.) Irie, R. F. (Div. Surg. Oncol., Univ. California Los Angeles); Morton, D. L. *Proc. Am. Assoc. Cancer Res.* 16:171; 1975.
- 6368 SPECIFICITY AND DISTRIBUTION OF ANTIGENIC DETERMINANTS ON THE POLYOMA VIRUS CAPSID AND NATURE OF THE REACTION OF IMMUNOGLOBULIN G ANTIBODY WITH THE CAPSID SURFACE. (Eng.) Kahan, L. (Dept. Physiological Chemistry, Univ. Wisconsin, Madison, Wis.); Fenton, W. A.; Murakami, W. T. *J. Mol. Biol.* 95(2):239-256; 1975.
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6377 T CELL LEUKEMIA IN CHILDREN [abstract]. (Eng.) Falletta, J. M. (Baylor Coll. Med., Houston, Tex.); Mukhopadhyay, N.; Starling, K. A.; Fernbach, D. J. *Clin. Res.* 23(1):66A; 1975.

6378 CHARACTERISTICS OF CYTOLYTIC T CELLS FROM RESISTANT AND SENSITIVE STRAINS IN MURINE LEUKEMIA [abstract]. (Eng.) Leclerc, J. C. L. (Hosp. Cochin, Paris, France); Gomard, E. J. *Proc. Am. Assoc. Cancer Res.* 16:202; 1975.

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6380 THE T-CELL NATURE OF THE LYMPHOCYTES IN TWO HUMAN EPITHELIAL THYMOMAS: A COMPARATIVE IMMUNOLOGIC, SCANNING AND TRANSMISSION ELECTRON MICROSCOPIC STUDY. (Eng.) Levine, G. D. (Stanford Univ. Medical Center, Stanford, Calif. 94305); Pollack, A. *Clin. Immunol. Immunopathol.* 4(2):199-208; 1975.

See also:

- * (Rev): 6021, 6023, 6024, 6025, 6026, 6027, 6032, 6036, 6045, 6046, 6047, 6050, 6065, 6066
- * (Chem): 6142, 6154, 6157
- * (Viral): 6238, 6244, 6247, 6254, 6259, 6264, 6273, 6280, 6281, 6351
- * (Path): 6469, 6473
- * (Epid-Biom): 6514, 6499

- 6381 REACTIVE PLASMOCELLULAR DYSCRASIA (IMMUNO-GLOBULINOPATHY) AND MYELOMA (CLINICO-MORPHOLOGICAL COMPARISONS). (Rus.) Alekseev, G. A. (Central Inst. Hematology and Blood Transfusion, Moscow, U.S.S.R.); Voyno-Iasenetskaia, O. V. *Klin. Med. (Mosk.)* 53(4):5-12; 1975.

Observations on the etiology and pathogenesis of myeloma are reviewed and cases are presented. Of 100 patients with multiple myeloma, 6 had a history of rheumatic heart disease. The malignant transformation of the first immunocyte may have taken place during the streptococcal antigen stimulation of the immunoglobulin-producing cell system. Chronic active hepatitis leading to cirrhosis, collagenoses, tuberculosis, syphilis, rheumatism, bronchial asthma, chronic autoimmune thyroiditis, autoimmune hemolytic anemia, desensitization for bronchial asthma and urticaria, and immune suppression therapy for kidney transplantation are described as possible precursors of multiple myeloma. Remarkably high incidence of multiple myeloma, Waldenstrom's disease, reticulosarcomatosis with macrocygoglobulinemia and Bence-Jones proteinuria were noted in patients with rheumatoid arthritis. The role of antigen stimulation of the immune globulin-synthesizing cell system as a primary push mechanism in the development of myeloma under the condition of genetic predisposition is suggested. In case of allergizing action of myeloma proteins (especially of Bence-Jones micromolecular globulins) at the early stage of development, myeloma manifests itself in the form of various clinical "traits" caused by tissue proteinosis. Bronchial asthma, observed in certain myeloma patients at the early stage of the disease without classical symptoms, may be interpreted as an early manifestation of the autoallergizing effect of myeloma proteins on the alveolar membranes.

- 6382 A CLINICAL STUDY OF THE NATURAL HISTORY OF LYMPHOSARCOMA AND RETICULUM CELL SARCOMA. (Eng.) Mukherji, B. (Sloan-Kettering Inst. for Cancer Res., New York, N.Y.); Yagoda, A.; Lee, B. J., III; Krakoff, I. H. *Eur. J. Cancer* 10(8):497-505; 1974.

To delineate the natural history and biologic behavior of lymphosarcoma (LSA) and reticulum cell sarcoma (RCS), the clinical records of all adult patients with LSA (76 cases) and RCS (112 cases) seen between January 1966 and June 1969 at a New York hospital were retrospectively reviewed. Determinations were made of the site(s) of disease involvement at diagnosis, the mode of initial disease presentation, the mode of progression and occurrence, therapy, and survival. Both LSA and RCS were most common in persons aged 41-70 yr, and the male to female ratio was 2:1 in LSA and 1.7:1 in RCS. Four major patterns of anatomic presentation were noted. The first was a localized form of disease presenting at a single node region or an extranodal site. The median survival of the nodal group was 56 mo for LSA and 33 mo for RCS; that of the extranodal group was 48 mo for LSA and 38 mo for RCS. The disease presented at extranodal sites, but was strictly confined within the abdominal cav-

ity in 9% of the LSA and 11.5% of RCS cases. The median survival was 16 mo for LSA and 12 mo for RCS. About half of the patients showing this pattern presented with diffuse disease involving multiple nodal and/or extranodal sites; the pattern appeared to be an entity uniquely suited for total abdominal irradiation. A form of the disease involving an extranodal site along with the corresponding node region was seen in 3% of LSA and 5% of RCS; initial disease presentation at two or more node regions on one side of the diaphragm was rarely seen. The third pattern of presentation was a generalized nodal pattern involving node regions both above and below the diaphragm. This pattern was observed in 40% of the LSA cases and 22% of the RCS cases, the median survival being 35 mo for LSA and 23 mo for RCS. A disseminated form of disease involving multiple nodal and extranodal site(s) was seen in over a third of the cases, and was associated with a very poor survival (seven months for LSA and six months for RCS). Recognition of the different patterns of anatomic presentation of LSA and RCS would be useful for the total management of these two non-Hodgkin's lymphomas.

- 6383 FAMILIAL LEUKEMIA. RECENT CASES AT THE PEDIATRIC CLINIC OF MODENA. (Ita.) Bertolani, M. F. (Istituto di Clinica Pediatrica dell'Università di Modena, Italy). *Clin. Pediatr.* 57(2):41-51; 1975.

Three cases of familial leukemia are presented. In the first case, three brothers presented with an acute lymphatic leukemia. Two became sick at the same time (one at 19 months and one at 15 yr) while the third brother became ill 8 yr later at the age of 18 months. His heterozygous twin sister remains in good health. In the second case, two second cousins died at the ages of 6 and 12 yr of acute lymphoblastic leukemia. Their siblings are all in good health as well as their parents; however, three of the grandparents died of neoplasia. In the third case, one brother became sick at the age of 2 yr and died 10 months later, while the other brother, leukemic at the age of 3 yr, is still alive. While the association in the same family of leukemia and other malignancies suggests a genetic predisposition, a purely genetic explanation is inadequate. With regard to monozygotic twins, there are cases where both siblings had leukemia, but there are also instances in which only one sibling had leukemia. The existence of familial leukemia and virological research suggest that aside from the family's genetic history, certain individuals are more sensitive to exogenous factors responsible for the onset of the disease (accidental factors such as viruses, radiation, or toxic factors).

- 6384 ASSOCIATION BETWEEN MYASTHENIA GRAVIS AND MALIGNANT LYMPHOMA. (Eng.) Levo, Y. (Beilinson Hosp., Petah Tikva, Israel); Kott, E.; Atsmon, A. *Eur. Neurol.* 13(3):245-250; 1975.

In support of the theory that autoimmune diseases, myasthenia gravis and malignancies have a common

pathological origin, a case is reported of a reticulum cell sarcoma in a 41-yr-old male with myasthenia gravis of 14-yr duration. The course of the myasthenia gravis had been intermittent with periods of marked muscular weakness treated with pyridostigmin (420-480 mg/day). While in a period of complete remission, the patient developed abdominal pains and was admitted to the hospital. Physical findings included palpable cervical lymph nodes and an enlarged spleen: biopsy of a node established the diagnosis of reticulum cell sarcoma. The patient experienced remission of the malignancy after one month of treatment with combined chemotherapy (cyclophosphamide, oncovin and prednisone). Myasthenia gravis has been considered an autoimmune disease of the thymus gland on the basis of immune reactions against muscle antigens correlated with disease severity and the 8-15% incidence of thymomas in patients with the disease. Malignancies associated with myasthenia gravis may also be a result of abnormal functioning of the thymus gland.

6385 THE PLATELET IN LEUKEMIC RETICULOENDOTHELIOSIS: FUNCTIONAL AND MORPHOLOGICAL EVIDENCE OF A QUALITATIVE DISORDER. (Eng.) Levine, P. H. (Tufts University, 171 Harrison Ave., Boston, Mass. 02111); Katayama, I. *Cancer* 36(4):1353-1358; 1975.

Platelets were studied in a group of ten patients (41-69 yr old; eight men and two women) with typical clinical course, morphological findings, and specific histochemical criteria for leukemic reticuloendotheliosis. Venous blood was centrifuged at $200 \times g$ to yield platelet-rich plasma; the remaining blood was then centrifuged at $850 \times g$ to yield platelet-poor plasma. Aggregation studies were performed on platelet-rich plasma using a turbidometric method. In eight patients, marked qualitative abnormalities were found in comparison with 60 healthy controls. These included lack of aggregation following epinephrine (0.2 ml of 1 mg/ml solution) stimulation (six patients), and decreased platelet factor 3 availability following ADP (0.1 ml of 10 mg/100 ml) solution stimulation (four patients). In addition, platelets in 4 of the 10 patients were studied by electron microscopy. All had granular abnormality, and one case showed the presence of rough-surfaced endoplasmic reticulum. The functional and ultrastructural abnormalities of platelets reported here may be responsible for the clinically important bleeding episodes which were not attributable to thrombocytopenia in two of the patients. The findings also provide a clue to the basic nature of this histogenetically controversial malignancy.

6386 THROMBOCYTHEMIC PRECURSORS OF CHRONIC MYELOID LEUKEMIA. (Fre.) Bauters, F. (Hopital A. Calmette, C.H.U. F 59033 Lille Cedex, France); Goudemand, M. *Nouv. Rev. Fr. Hematol.* 15(2):241-244; 1975.

The thrombocytic precursors of chronic myeloid leukemia (CML) were studied; the rise in plate-

lets was highly significant, contrasted with a moderate hyperleukocytosis, and dominated the early stages, resembling an idiopathic thrombocytopenia (IT). The detection of CML on this basis is rare and occurred in four of the 250 cases studied. In all four, hyperleukocytosis was moderate ($14,800-29,200 \text{ WBC/mm}^3$) with neutrophilic polynucleosis and medullosis (6-21%). Leukocytic alkaline phosphatase was nonexistent or strongly inhibited. Thrombocytopenia was permanent and varied between $1,200,000$ and $2,200,000/\text{mm}^3$. Bone marrow biopsy detected a myeloid hyperplasia without collagenic fibrosis. The Philadelphia chromosome (Ph1) was repeatedly detected in bone marrow karyotype studies. Treatment consisted of busulfan (2-4 mg/day) and was administered at the time of thrombocytic manifestations. One patient (a man, 52 yr old) died of enterobacterial septicemia after three months. Case II (a woman, 58 yr old) suffered an acute myeloblastic transformation one year after diagnosis, was stabilized with 6-mercaptopurine and hydroxyurea, and died after two years, 11 mo. Case III (a woman, 60 yr old) suffered an acute myeloblastic transformation 16 mo after the detection of the first hematologic symptoms, and died after two years, nine months. Case IV (a man, 72 yr old) died four years, seven months following a cardiac arrest. Initial symptomatology was very similar to that of IT. The essential factor which makes possible a confirmation of a CML diagnosis is the Ph1 chromosome. The karyotype is usually normal in cases of IT aside from the possible presence of a nonspecific aneuploidy and extra chromosomes. The diagnosis of thrombocytic precursors of CML and the distinction from IT is prognostically significant since in the former case acute myeloblastic transformation is common whereas real ITs are characterized by a very long stabilization with ^{32}P or busulfan and infrequently display a terminal acute state. Other factors which support a thrombocytic precursor diagnosis of CML are a constant myeloma above 5%, and the low activity of the phosphatases.

6387 HAIRY CELL LEUKEMIA: FUNCTIONAL, IMMUNOLOGIC, KINETIC, AND ULTRASTRUCTURAL CHARACTERIZATION. (Eng.) Debusscher, L. (Service de Medecine et d'Investigation Clinique, et la Service de Chirurgie de l'Institut Jules Bordet, Centre des Tumeurs de l'Universite Libre de Bruxelles, Belgium); Bernheim, J. L.; Collard-Ronge, E.; Govaerts, A.; Hooghe, R.; Lejeune, F. J.; Zeicher, M.; Stryckmans, P. A. *Blood* 46(4):495-507; 1975.

A diagnosis of hairy cell leukemia in a 51-yr-old man was made by optic microscopy, phase-contrast microscopy, electron microscopy, scanning microscopy, and histochemistry of the abnormal blood cells. *In vivo* these cells were found to have a half-time in the blood of about 150 hr. *In vitro* they had the capacity to adhere firmly to plastic, making it possible to obtain a pure population of hairy cells. Neither T-rosette formation nor phytohemagglutinin transformation could be demonstrated in these cells. On the other hand, the presence of

immunoglobulins (Ig) on the surface of the hairy cells by immunofluorescence, and the synthesis and secretion by these cells of IgM type λ -chains shown by radioimmunodiffusion, were in favor of their B-type lymphocyte origin. Similarities to chronic lymphocytic leukemia were apparent in the half-time of the hairy cells and in the nature of the synthesized Ig. It remains to be determined whether the morphology of the hairy cells represents merely an unusual expression of the neoplastic process of B lymphocytes or the expression of a special function of a lymphocyte subclass or differentiation stage.

- 6388 THE PLATELET DEFECT IN LEUKEMIA: PLATELET ULTRASTRUCTURE, ADENINE NUCLEOTIDE METABOLISM, AND THE RELEASE REACTION. (Eng.) Cowan, D. H. (Case Western Reserve Univ. Sch. Medicine, Cleveland, Ohio); Graham, R. C., Jr.; Baunach, D. *J. Clin. Invest.* 56(1):188-200; 1975.

The ultrastructure and adenine nucleotide metabolism of platelets from nine patients with acute (nonbleeding) leukemia were studied to elucidate mechanisms for the platelet dysfunction observed. Nonstimulated (resting) platelets from leukemic patients varied greatly in size; exhibited marked variation in the number of alpha granules present per cell; had poorly delineated circumferential bands of microtubules; and often grossly dilated open channel systems or cytoplasmic vacuolization. The intracellular concentrations of ATP and ADP were significantly below normal. The specific radioactivity of ATP from [14 C]adenine by nonstimulated platelets in leukemia was 6,861 cpm/nmole, compared to 4,923 for stimulated normal platelets. A similar effect was found for radioactivity in ADP ($p < 0.05$). Addition of ADP or soluble collagen to platelets from leukemic patients was followed by retarded and incomplete shape change, delayed and incomplete centripetal migration of subcellular organelles, impaired degranulation, and the formation of loose aggregates composed of relatively few platelets. Stimulation of "leukemic" platelets with collagen led to the release of significantly subnormal amounts of ATP and ADP and no significant change in the specific radioactivity of the intracellular nucleotides. In contrast to normal platelets, the conversion of ATP to inosine monophosphate and hypoxanthine in platelets in leukemia failed to increase significantly with collagen stimulation. Abnormalities exist in the storage pool of adenine nucleotides and the release mechanism of platelets in acute leukemia. These defects appear to contribute to an impairment in the release reaction in these platelets. Many of the ultrastructural and metabolic defects seen in acute leukemia occur in platelets in preleukemia.

- 6389 SARCOMA SIMULATING OSTEOMYELITIS IN SICKLE CELL ANEMIA. (Eng.) Fisher, B. (Veterans Administration Hosp., 3405 Bailey Ave., Buffalo, N.Y. 14215). *Wadley Med. Bull.* 5(4):367-371; 1975.

A man with homozygous (S-S) sickle cell disease

developed a primary bone tumor in his left tibia at age 42 yr. Differentiation from osteomyelitis was possible only by biopsy, which revealed diffuse infiltration by irregular, spindle-shaped cells with hyperchromatic nuclei and prominent nucleoli. No new bone formation was seen, but the tumor invaded the marrow space. The patient presented with pain and localized swelling of short duration. X-rays of the tibia had shown a lytic lesion at the site of an old bone infarction and small areas of periosteal involvement. Above-knee amputation was carried out without complications. However, the patient died within a year with pulmonary and cerebral metastases. Although the association of neoplastic disease with sickle cell anemia appears to be infrequent, it is possible that the incidence of malignancies may increase since patients with sickle cell disease are now surviving into the fifth and sixth decades of life.

- 6390 CARCINOMA AND EPITHELIAL DYSPLASIA COMPLICATING ULCERATIVE COLITIS. (Eng.) Cook, M. G. (General Infirmary at Leeds, Leeds, England); Goligher, J. C. *Gastroenterology* 68 (5/Part 1):1127-1136; 1975.

The pathology of 19 specimens of carcinoma complicating ulcerative colitis was reviewed with particular reference to the incidence of epithelial dysplasia. Thirteen patients had one carcinoma, five patients had two carcinomas, and one patient had three. Of the 26 carcinomas, 13 were producing abundant mucin. Only five carcinomas were typically nodular and ulcerated. The proportion of poorly differentiated tumors complicating ulcerative colitis (8 of 26) was not as high as previously reported. Of the patients in the series, 26% are alive and well at least five years after surgery. Unequivocal epithelial dysplasia was demonstrated in some part of the large intestine in 15 of 19 specimens with colitis carcinoma, but was also found in 4 of 14 specimens from a "control" series of patients with longstanding total colitis but without carcinoma. Thus, the finding of dysplasia in a rectal biopsy of a patient with colitis is not a reliable guide to the presence of a frank carcinoma elsewhere in the bowel. The fact that epithelial dysplasia when present in colitis is often patchy in distribution and frequently spares the rectum even in patients with definite carcinomas makes a negative rectal biopsy particularly unreliable in deciding on the absence of a tumor or the lack of predisposition to it. Multiple biopsies from different parts of the colon as well as the rectum would thus seem to be desirable if mucosal sampling is to be employed as a screening test.

- 6391 POLYPOSIS IN ULCERATIVE COLITIS. (Eng.) Teague, R. H. (Bristol Royal Infirmary, Bristol, England); Read, A. E. *Gut* 16(10):792-795; 1975.

One hundred and fifty cases of ulcerative colitis were assessed by total colonoscopy with multiple

biopsies. Inflammatory polyposis was found in 25 (17%) cases, and six of these had a large (>1.5 cm) solitary polyp which radiologically resembled carcinoma in four cases. Adenomatous polyps were discovered in four cases, and three of these were solitary. Three carcinomas were found at endoscopy, of which two were entirely unsuspected. In all cases endoscopic polypectomy or surgical intervention was performed to establish the exact histological diagnosis. The advent of total endoscopic examination of the bowel in ulcerative colitis means that colectomy can in some cases be avoided or at least delayed until the clinician is sure that the patient would definitely benefit from this procedure.

6392 PATHOGENESIS OF POLYPOUS LESIONS OF THE LARGE INTESTINE IN CHILDREN. (Rus.)

Malyshv, Iu. I. (D. I. Ul'ianov Kuibishev Medical Inst., Kuibishev, USSR); Katorkin, E. N.; Pyt'eva, G. P. *Pediatrics* (6):30-32; 1975.

The biochemical, morphological and pathogenetic aspects of polyps of the large intestine were studied in 171 children aged 3-15 yr., including 87 boys and 84 girls. Solitary polyps were found in 44 patients, groups of polyps in 50 patients, multiple polyps in 74 patients, and diffuse polyposis of the large intestine in three patients. Predominantly acid reaction of the feces and increased organic acid content at normal ammonia levels were found in 60 patients. Atrophic and dystrophic changes suggestive of the morphological syndrome of chronic jejunitis were found in biopsy samples taken from seven patients. Inborn or acquired pathology of the small intestine is believed to be one of the factors of the chronic lesion. The dystrophic and atrophic changes of the mucosa lead to disturbances in digestion, and the dyskinesia of the small intestine results in the passage of a considerable amount of insufficiently hydrolyzed matter into the large intestine. The essential changes in the physicochemical properties of the chyme lead to a pathological regeneration of the large intestinal mucosa with polyp formation. The polypous lesion of the large intestine is consequently assumed to be the morphological manifestation of the adaptation of the large intestinal mucosa to the changes in the physicochemical properties of the contents of this intestine.

6393 IgA ASSOCIATED LYMPHOPLASMACYTIC TUMOR INVOLVING THE CONJUNCTIVA, EYELID, AND ORBIT. (Eng.) Jampol, L. M. (Yale Univ. Sch. Med., New Haven, Conn.); Marsh, J. C.; Albert, D. M.; Zimmerman, L. E. *Am. J. Ophthalmol.* 79(2):279-284; 1975.

A case history is presented of a 65-yr-old man who had an unusual conjunctival, eyelid, and orbital tumor associated with sc masses and lymph node involvement. The tumor first appeared in the subconjunctival tissues of the right eye and was treated with orbital irradiation. There was complete clinical regression of the mass and the patient remained

well for more than 3 yr when he noted the onset of masses in the left epigastric area, right inguinal area and the right buttocks. Biopsy showed lymphosarcoma with extensive amyloid and para-amyloid deposits. Radiotherapy again resulted in regression of the masses. The patient continued to have cycles of recurrence, local incision and radiotherapy, and regression for 11 yr. The results of a hemogram, blood urea nitrogen, serum creatinine, liver function tests, serum calcium, and serum phosphorus were all normal. Heat and acetic acid tests of urine for Bence Jones protein were negative on two occasions. Serum immunoelectrophoresis revealed a monoclonal immunoglobulin A (IgA) spike. Histologically and clinically, there were similarities to both plasma cell and lymphocytic neoplasms. Prominent intranuclear inclusions, or Dutcher bodies, were present in the tumor cells. It is concluded that this tumor does not fit into the category of multiple myeloma but instead represents a malignant sarcoma with plasmacytoid lymphocytes.

6394 HYPERCALCEMIA AND NEOPLASIA: BIOLOGIC, BIOCHEMICAL, AND ULTRASTRUCTURAL STUDIES OF A HYPERCALCEMIA-PRODUCING LEYDIG CELL TUMOR OF THE RAT. (Eng.) Rice, B. F. (Alton Ochsner Medical Foundation, 1520 Jefferson Highway, New Orleans, La. 70121); Roth, L. M.; Cole, F. E.; MacPhee, A. A.; Davis, K.; Ponthier, R. L.; Sternberg, W. H. *Lab. Invest.* 33(4):428-439; 1975.

Further biologic, biochemical, pharmacologic, and morphologic information about a unique spontaneous testicular tumor found in an aged inbred Fischer rat are presented. Sixty Fischer rats were used in the study. Tumor suspension was transplanted into intact male, intact female, castrated male, and oophorectomized female rats. Cross examination of the tumor showed a circumscribed gray soft multinodular mass with areas of cystic degeneration and hemorrhage. Light microscopy revealed a moderately differentiated Leydig cell tumor. Electron microscopically, the tumor was composed of fairly large polygonal cells, granular endoplasmic reticulum, and numerous prominent microvilli; it was deemed less differentiated than known steroid-secreting cells. The small seminal vesicles and ventral prostates, or small uteri observed in the gonadectomized tumor-bearing animals suggested a lack of secretion of any potent sex steroids. Biochemical studies on steroid hormone identification using [1-¹⁴C]-acetate resulted in a failure to identify any steroids produced by gonadal tissues. Using ¹⁴C-radioactivity and gas liquid chromatography, campesterol, stigmasterol, and β -sitosterol were tentatively identified. Further studies on the C₂₇ zone of thin layer chromatograms revealed traces of ¹⁴C associated only with the phytosterols. In receptor binding studies, only trophic hormones possessing luteinizing hormone activity were able to compete with [¹²⁵I]-human chorionic gonadotropin (HCG) for binding to the tumor homogenate. *In vivo* clearance studies revealed increased phosphorus and calcium excretion in castrated and thyroparathyroidectomized castrated tumorbearing rats, despite a declining creatinine clearance. Among 18 intra-

splanic transplants, only those which developed adhesions to the spleen became hypercalcemic. While ip injection of 500 IU HCG caused a rapid rise in the serum calcium of the tumorbearing rats, iv cortisol phosphate (10 mg) lowered serum calcium, as did conjugated estrogens and AY-9944. The cumulative data indicate that the hypercalcemia-producing tumor is of Leydig cell origin, which secretes a small molecular weight, rapidly metabolized, calcium-mobilizing substance.

- 6395 THE CELL PROLIFERATION OF EPITHELIAL METAPLASIA IN THE PROSTATE GLAND: AN AUTORADIOGRAPHIC *IN VITRO* STUDY. (Eng.) Helpap, B. (Pathologisches Institut der Universität Bonn, D-5300 Bonn-Venusberg, Postfach, West Germany); Stiens, R. *Virchows Arch. [Zellpathol.]* 19(1): 69-76; 1975.

From material of prostate biopsies, which were incubated with radioactive thymidine, experiments were made to determine whether differences in cell kinetics exist between squamous and transitional epithelial metaplasias in the prostate. In 147 autoradiographically examined prostate biopsy cylinders 5.4% squamous metaplasia and 6.0% transitional metaplasia were diagnosed. The average labeling index of squamous metaplasia was 4.3% and corresponded with values from nonkeratinizing squamous epithelium in other locations. The labeling index of the transitional cell metaplasia was, in contrast, almost ten times lower with an average value of 0.29% and corresponded with the values well known for the urothelium of the urinary bladder. Higher labeling indices were observed in two cases but these had chronic prostatitis. The autoradiographic results are in good agreement with the ultrastructural findings in which the metaplastic squamous epithelium corresponds with normal squamous epithelium. Cellular proliferation takes place only in the basal stratum. Transitional metaplasia, however, exhibits DNA-synthesizing cells in the superficial cell layers, as in the urothelium. The extent to which the duration and dosage of the estrogen therapy can influence the intensity of the cell proliferation within the squamous metaplasia cannot be finally estimated. However, the patient who had the lowest labeling index of 0.7% received only one dose of estrogen whereas a long time estrogen therapy was received by all other patients with squamous metaplasia.

- 6396 ENDOMETRIAL TUMORS AND/OR ASSOCIATED CARCINOMAS OF PROSTATE. (Eng.) Tannenbaum, M. (630 West 168 St., New York, N.Y. 10032). *Urology* 6(3):372-375; 1975.

Endometrial neoplasms of the prostate were uropathologically categorized. The majority of the cases histologically recognized were seen as papillary masses present in the region of the verumontanum. All tumors occurred in phenotypically normal male patients. While the majority were associated with the more conventional microacinar carcinomas of

the prostate, there was also a transitional cell carcinoma of the bladder and an association with a tumor of the periurethral ducts. This type of endometrial growth can exhibit several histologic patterns. All the exophytic masses in the prostatic urethra, in situ, or spreading up the ducts have cells with eosinophilic nucleoli and cytoplasm, and nuclei with a peripheral clumped chromatin pattern. The cells sometimes had numerous mitotic figures, fibrovascular stalks, and/or sparse lymphocytic infiltrates. In a more benign variant endometrial glands were surrounded by a lamina propria with numerous inflammatory cells. A well differentiated carcinoma of the prostate is a more biologically aggressive tumor type. While the histologic varieties and gross pathology of the endometrial growths were more indicative of a nonmetastasizing neoplasm, associated contiguous prostate carcinomas were noted to possess a metastasizing potential. A recommendation of preferentially treating the more biologically aggressive tumor, i.e. prostate carcinoma of microacinar type, is presented.

- 6397 EARLY MALIGNANT CHANGES IN PLEURAL PLAQUES DUE TO ASBESTOS EXPOSURE: A CASE REPORT. (Eng.) Lewinsohn, H. C. (TBA Industrial Products, Rochdale, England). *Br. J. Dis. Chest* 68:121-127; 1974.

The autopsy findings for a 53-yr-old former asbestos (chrysotile and crocidolite) worker showed discrete nodules of mesothelioma arising from both visceral and parietal pleural surfaces. The case shows that fof mesothelioma can arise from pleural cells overlying a hyaline plaque. The series of chest radiographs of this patient, the first 19 yr before autopsy, indicate a possible origin of a mesothelioma in noncalcified pleural plaques.

- 6398 NUCLEAR MORPHOLOGY IN FALSE NEGATIVE AND NEGATIVE RECTAL BIOPSIES. (Ita.) Rilke, F. (Servizio di Anatomia e Istologia Patologica dell'Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy); Clemente, C.; Pilotti, S. *Tumori* 61(2):199-209; 1975.

The nuclear morphology in false negative and negative rectal biopsies is described. An atypical nuclear structure (ANS) consisting of a cribriform and condensed chromatin pattern with hyperchromasia, a small nucleolus, and a moderately increased nuclear-cytoplasmic ratio was observed in the epithelial cells of the crypts and in the stroma and muscular cells of 51 of 70 oncologically negative biopsies of the rectal mucosa. The subsequent retrieval of all clinical and histological data revealed that the 51 cases included 39 adenocarcinomas of the large intestine either present at a variable distance from the false negative biopsy (15 cases) or removed previously (24 cases), 7 extra-intestinal malignant tumors (parotid gland, urinary bladder, endometrium, breast, stomach, and anus), and 5 benign lesions of the large intestine. Of the remaining 19 cases whose biopsies did not reveal the ANS, 16 had benign lesions of the large

intestine, 2 had an adenocarcinoma of the large intestine (1 present and 1 removed previously), and 1 carcinoma of the anus. In the rectal biopsies, the ANS was detected in 93.9% of cases of a malignant tumor either present or removed previously, and 19% of the cases of benign lesions. The identification of these nuclear structures is of potential value from a histopathological point of view in evaluating negative rectal biopsies, and in being indicative of the need for a second biopsy, since approximately 80% of the patients with ANS had a malignant tumor of the large intestine. The morphologic evidence indicates that the ANS is compatible with a possible disturbance of the mitotic cycle since the findings were restricted to the proliferating zone of the rectal epithelium. The presence of cells with deformed nuclei in benign areas, at a certain distance from the neoplasia, could be correlated with the general involvement of the host during the development and growth of the tumor.

6399 COLUMNAR-LINED LOWER ESOPHAGUS: AN ACQUIRED LESION WITH MALIGNANT PREDISPOSITION--REPORT ON 140 CASES OF BARRETT'S ESOPHAGUS WITH 12 ADENOCARCINOMAS. (Eng.) Naef, A. P. (Yverdon Hosp., 1400 Yverdon, Switzerland); Savary, M.; Ozzello, L. *J. Thorac. Cardiovasc. Surg.* 70(5): 826-835; 1975.

From 1963 to 1975, 6,368 esophagoscopies were performed by one of the authors at several medical and surgical departments. The article demonstrates that columnar-lined lower esophagus (CLLE) is an acquired condition with a possible etiologic relationship to esophageal adenocarcinoma. The number of reflux esophagitis cases was 1,225; of these, 140 were extensive columnar metaplasias of the distal metaplasia. Extensive CLLE represents a late irreversible stage of reflux esophagitis. Repeated esophagoscopies demonstrate the acquired nature of the lesion. It is caused by the progressive healing, from below upward, of peptic ulcerations on the squamous epithelium by metaplasia of columnar mucosa. Antireflux operations stop the progressive ascent of heterotopic epithelium and thus stabilize reflux esophagitis and cure complications such as ulcerations and strictures. The premalignant character of this condition is established by a 10% incidence of adenocarcinomas in a series of 140 cases of extensive columnar metaplasia. The transition toward malignancy seems to be irreversible and cannot be arrested by an antireflux operation. Therefore, repeated esophagoscopic controls and biopsies are an absolute necessity in all cases of extensive columnar metaplasia, even after cure of active reflux esophagitis by Nissen fundoplication.

6400 DISTINCTIVE INTESTINAL MAST CELL NEOPLASMS OF DOMESTIC CATS. (Eng.) Alroy, J. (Rush Medical Sch., 1752 West Congress Pkwy., Chicago, Ill. 60612); Leav, I.; DeLellis, R. A.; Weinstein*, R. S. *Lab. Invest.* 33(2):159-167; 1975.

The pathology of a group of 24 mast cell tumors, arising in the intestine of domestic cats, that are

morphologically distinct from other mast cell tumors in this species, were investigated by histologic, histochemical, and ultrastructural techniques. Specimens were fixed in 10% formalin, sectioned at 4-8 μ m, and stained with hematoxylin and eosin. Three well- or moderately well-differentiated feline mast cell tumors from skin and three similar tumors from viscera other than intestine were examined for comparison. Tissues for ultrastructural studies were obtained from a primary intestinal tumor and mesenteric lymph node metastases and from a typical visceral feline mast cell tumor arising in the spleen. Sections of Epon embedded tissues were stained with toluidine blue for light microscopy. Thin sections (50-70 nm) were stained with uranyl acetate and lead citrate for electron microscopy. Twenty-one of the tumors originated in the small intestine and three in the colon. Neoplastic cells were either in nests separated by delicate strands of collagen or in whorls; these patterns occurred with equal frequency. Cells in the six control mast cell tumors were arranged in sheets and were similar in size to those found in the intestinal neoplasms. Two of the six intestinal neoplasms studied with special stains contained clusters of neoplastic cells with strongly reactive metachromatic granules. In the remaining cases, occasional metachromatic positive cells were dispersed among vacuolated negative cells. Size, shape, and nuclear morphology were identical for cells with and without metachromatic granules. Many intestinal mast cell tumor cells, in the current series, had the typical ultrastructure of degranulated mast cells. None of the tumor cells examined by electron microscopy contained electron-dense or crystalline mast cell granules which are a component of normal and neoplastic mast cells in other organs of cats. Many granules in the intestinal tumors were morphologically identical with those described in mast cells in several species. There were moderate numbers of microvilli at the cell surface. The cytoplasm contained free ribosomes and elements of rough endoplasmic reticulum. Mitochondria were small and round or oval. Ulceration did not occur in any of the intestinal mast cell neoplasms, suggesting that neoplastic cells may either be deficient in, or entirely lacking, the vasoactive substance. It is suggested that the differences between the cells in the typical visceral and intestinal tumors confirm the existence of morphologic and functionally heterogeneous populations of mast cells occurring in different anatomical locations of the body.

6401 PROGNOSIS OF MAMMARY CARCINOMA IN YOUNG WOMEN. (Eng.) Gogas, J. (King Paul's Hosp., Athens, 609, Greece); Skalkas, G. *Surgery* 78(3):339-342; 1975.

The records of 162 women with carcinoma of the breast, age 40 yr or younger and treated between 1950 and 1969, were reviewed to evaluate the prognosis in young women. The 5-yr survival rate among patients 20-35 yr of age (50%) was slightly higher than that in patients 36-40 yr old (46%). In stage B and more advanced breast cancer in young women, the outlook was poorer than in women

41 yr and older. When axillary involvement was present during gestation or in the immediate postpartum period, the prognosis was especially poor. The women in this study had an unusually high proportion (35%) of low-grade, infrequently metastasizing tumors such as medullary, intraductal, papillary, and lobular carcinomas. The presence of cancer in the axillary nodes at mastectomy was the most important factor affecting prognosis in mammary cancer. There is evidently no reason to consider carcinoma of the breast in young women a more lethal disease than that seen in their older counterparts.

- 6402 MELANOGENESIS IN HUMAN MELANOMAS.
(Eng.) Chen, Y. M. (Dept. Biol., Wayne State Univ., Detroit, Mich.); Chavin, W. *Cancer Res.* 35(3):606-612; 1975.

Fifteen different human primary melanomas were utilized to observe melanogenesis in human melanomas. Each melanoma was grouped according to the degree of melanogenesis. Net tyrosinase activity, evaluation of L-tyrosine conversion, and the incorporation of L-tyrosine carboxyl groups into medium were determined. Resolution of tyrosinase isoenzymes was determined by the modified method of disc gel electrophoresis. Subcellular distribution and total tyrosinase present in a homogenate was used to determine enzymatic activity and endogenous inhibition of such activities. Tyrosinase activity was found to be dependent on the degree of melanization. Extremely high tyrosinase activity was detected in melanotic human melanomas, amelanotic myeloma activity was the same as that found in caucasian breast skin while partially melanotic melanoma fell between the two preceding extremities. Soluble tyrosine occurred only in melanotic melanomas and was found to have a varying fraction of total tyrosinase present. Electrophoresis patterns of tyrosinase isoenzyme were suggested to be similar to T¹ and T² enzymes found in mammalian melanomas. Two inhibitors were found: (1) Inhibitor 1 (soluble fraction) found in partially melanotic melanoma; and (2) inhibitor 2 (lipase digested particulate fraction) found in melanotic melanoma. Inhibition of tyrosinase activity may produce regression of abnormal cell growth, suggesting an approach to melanoma chemotherapy.

- 6403 TRANSFORMATION OF A MALIGNANT MELANOMA *IN VITRO*. CHROMOSOMAL STUDY. (Fre.)
Berger, R. (Centre de Recherches Biologiques Neoplasiques (U 29 INSERM), 123, boulevard de Port-Royal, 75014 Paris, France); Aubert, C. *C. R. Acad. Sci. D. (Paris)* 280(20):2409-2412; 1975.

Chromosomes of cells from two *in vitro* cultured lines, IGR 23 which is fibroblast-like and IGR 22 with well-differentiated melanocytes, derived from a single primitive melanoma, are compared. The fibroblast-like cells of IGR 23 undergo spontaneous transformation into differentiated cells when cultured in medium from IGR 22. Karyotyping and

staining of chromosomal bands G, Q, C and R revealed characteristic marker chromosomes in the cell line IGR 22. The fibroblast-like cell line IGR 23 had two cell populations: the majority of cells carried abnormal marker chromosomes identical to those of IGR line 22; a minority cell population was normal. The blood karyotype of the patient with the original melanoma was that of a normal female. After the cells in line IGR 23 underwent transformation into differentiated melanocytes, only cells with marker chromosomes were observed. Despite the fibroblast-like phenotype of cell line IGR 23, chromosome analysis revealed that the majority of cells are identical to those in the differentiated cell line IGR 22. It is postulated that a diffusible factor in the culture medium of the melanocyte cells supports growth of cells with abnormal chromosomes.

- 6404 CARCINOIDS AND CANCEROUS DIATHESIS. (Fre.)
Giroux, L. (Hopital Notre-Dame, 1560 est, rue Sherbrooke, Montreal, Canada); Laurencelle, L.; Lesage, R.; Delorme, F. *Union Med. Can.* 104(4):596-600; 1975.

The association between a carcinoid tumor of the digestive tract and subsequent cancers is investigated. A statistical study of 124 carcinoids of the digestive tract indicated that when the first tumor is a carcinoid of the digestive tract, whether it originates from the appendix or from the small intestine, there is a higher incidence of a second cancer. The 124 cases examined included carcinoids located in the stomach (1), the small intestine (21), the colon (2), the appendix (94), and the rectum (7). The average age for small intestine carcinoids was 64.3 yr, 40.3 yr for the appendix, and 47.1 yr for the rectum. Small intestinal carcinoids were more prevalent in men (88%) and appendix carcinoids were more so in women (86%). Twenty-one patients had at least one second cancer; the general incidence of multiple cancers in the same patient was 2.8%. Second cancer appeared in 38% of patients with carcinoids of the small intestine, and in 12% of patients with carcinoids of the appendix. There was no predominance of a particular type in the second cancers. Although the statistical findings cannot confirm the association of a cancerous diathesis with carcinoids of the digestive tract, they are sufficient to warrant special attention to follow-up patients with a diagnosis of a carcinoid tumor of the digestive tract.

- 6405 CARCINOID TUMORS: AN ANALYSIS OF 2837 CASES. (Eng.) Godwin, J. D., II (Nat'l. Cancer Inst., Bethesda, Md. 20014). *Cancer* 36(2):560-569; 1975.

Incidence rates of carcinoid tumors were studied based on a statistical analysis of 2,837 cases of carcinoid tumors. Tumors were found in the lung, ovary, and biliary and gastrointestinal tracts, the most common sites being the appendix, rectum, and ileum. The carcinoid tumors differed from other malignancies with respect to male to female and black to white ratios, distribution by anatomi-

cal site, and patient age. For all sites but the lung and appendix, carcinoid tumors were more common in blacks than in whites, and for all sites but the appendix, rates for males were higher than those for females. Except for lung carcinoids, the rates were highest in black males. The average ages of affected patients were low for the appendix, rectum and rectosigmoid, lung, and bronchi; the average age was higher for the stomach, small intestine, and colon. The percentages of concurrent neoplasms and multiple carcinoids were low compared with other carcinoid series. Most concurrent neoplasms were located in the gastrointestinal tract or uterus, and the small intestine was a common location for the few multicentric carcinoids observed. Forty-one percent of the carcinoid tumors were coded as malignant, survival not being well predicted by the histologic assessment of malignancy. The first course of therapy was surgery in 88% of the cases, particularly in those cases involving localized carcinoids. Five-year survival rates ranged from 99% (appendix) to 33% (sigmoid colon), the latter showing the highest percentage of metastases. There were few differences in survival by race, sex, or age. The data suggest that carcinoid tumors differ from noncarcinoids with respect to etiologic agent(s) and/or host and site susceptibilities. Lung carcinoids may differ from other carcinoids in these respects also.

6406 OAT CELL CARCINOMA OF THE BRONCHUS AND THE CARCINOID SYNDROME. (Eng.) Salyer, D. S. (Johns Hopkins Hosp., Baltimore, Md. 21205); Eggleston, J. C. *Arch. Pathol.* 99(10):513-515; 1975.

A case report of a 67-yr-old man with oat cell carcinoma of the bronchus and carcinoid syndrome is presented. The patient was a heavy smoker and presented with a history of two syncopal attacks, increased abdominal girth, anorexia, weakness, diarrhea, vomiting and abdominal tenderness. Physical examination showed him to be jaundiced with hepatomegaly, ascites, and dependent pitting edema. Electrocardiogram showed premature atrial, nodal and ventricular contractions. Chest X-ray showed pulmonary edema only. Urine analyses for 5-hydroxyindoleacetic acid was strongly positive. Liver biopsy showed metastatic small cell undifferentiated carcinoma compatible with a bronchogenic primary tumor. At autopsy, a 3-cm small cell undifferentiated carcinoma was found in the left upper lobe bronchus. The tumor cells were small and pleomorphic, with hyperchromatic nuclei, scanty cytoplasm and numerous mitoses. Local and distant metastases were present; however, none were seen in the gastrointestinal tract. Focal endocardial thickening of the right atrium, the ventricle, and the tricuspid valve were also noted; these findings in the heart are characteristic of serotonin-producing tumors. Low levels of serotonin were found in the tumor itself, but it is believed that either the tumor secreted or did store serotonin, or that assay was performed too late. Previous studies have shown granules in oat cell carcinomas of the lung that are identical to those of carcinoids, and serotonin-producing oat

cell carcinomas have been previously described. Both oat-cell and bronchial carcinoids arise in organs of endodermal derivation and both are thought to originate from neural crest cells. The histologic and ultrastructural similarities between bronchial carcinoids and oat cell carcinomas suggests that the latter is a very malignant tumor arising from the argentaffin cells of the lung.

6407 ON THE RELATIONSHIP OF CHOLELITHIASIS TO CARCINOMA OF THE GALL-BLADDER AND ON THE SEX DEPENDENCY OF THE CARCINOMA OF THE BILE DUCTS: A STUDY BASED ON THE AUTOPSY DATA FROM 1928 TO 1972. (Eng.) Parkash, O. (IInd Surgery Dept., Wilhelminenspital der Stadt Wien, 16 Montleiarstrasse 37, A-1171 Wien, Austria). *Digestion* 12(3):129-133; 1975.

In order to clarify the relationship between gallstones and gallbladder carcinoma, 60,000 autopsy records derived from Vienna for 1928-1972 were studied. In the non-cancer autopsy population the incidence of cholelithiasis is 17.1 and 37.5% for males and females, respectively; in the cancer population the corresponding figures are 73.6 and 73.0%. ($P < 0.001$). In both sexes cholelithiasis is more frequent when the carcinoma of the gallbladder is present simultaneously. Other studies indicate that only 1-2% of cholelithiasis cases ever develop gallbladder carcinoma. In males, 50.2% of malignancies affect the bile ducts and 49.8% affect the gallbladder. In females, 23.8% of malignancies affect the bile ducts and 76.2% affect the gallbladder ($P < 0.001$). Gallstones appear to have no direct etiological relationship with this carcinoma. Prophylactic cholecystectomy is not indicated.

6408 BEHAVIOUR OF WILMS TUMOUR AND NORMAL METANEPHROS IN ORGAN CULTURE. (Eng.) Rousseau, M. F. (INSERM U 77, Hospital Necker Enfants Malades, 149 rue de Sevres, 75730 Paris Cedex 15, France); Nabarra, B.; Nezelof, C. *Eur. J. Cancer* 10(8):461-466; 1974.

To study the process of differentiation in nephroblastoma or Wilms' tumor, the behavior of 40 such tumors grown in organ culture was investigated. The tumors, 34 of which were primaries, were derived from 18 girls and 22 boys less than seven years old. Ten metanephros from 3 to 4-mo-old human fetuses served as controls. Some of the cultures were treated with ^3H -thymidine (20 $\mu\text{Ci}/\text{mM}$) and were examined by autoradiography; in addition, the cultures were studied by light and electron microscopy. Of the Wilms' tumors, two were completely undifferentiated, nine contained a few differentiated tubules in a mesenchymatous type of basic stroma, 11 showed glomerular precursors, and 18 showed striated or smooth muscle differentiation. Irradiation in the case of the six recurrent tumors produced necrotic changes and a tendency toward muscle differentiation. Neither the tumor explants nor the normal fetal kidney increased in size during *in vitro* culture. De-

pending on the histological type of the tumor, its condition when removed, and on the patient's age, central necrosis of some of the histological structures and encapsulation were observed after varying periods of time in culture. Survival was increased in the nonirradiated compared with the irradiated tumors, in tumors from children less than two years of age, and in the epithelial elements. Electron microscopy revealed a tendency toward fibroblastic transformation of all elements of the stroma during culture, accompanied by an increased amount of fibrous degeneration. Both the fibroblasts and large isolated cells had numerous vacuoles or large lipid inclusions. Large vacuoles full of necrotic waste matter appeared in the cell masses within as little as one week; myelin figures also appeared, and the nuclei became pyknotic. The tubular structures were less rapidly affected by necrosis, whereas the muscular fibers lost their characteristics and became amorphous. A pre-glomerular formation was observed after one week in culture. The results indicate that the survival of neuroblastomas in organ culture depends greatly on the degree of differentiation, the behavior of most differentiated tumors being similar to that of normal developing kidney.

- 6409 HISTOPATHOLOGICAL STUDY OF SIX CASES OF CASTLEMAN'S TUMOR. (Eng.) Harigaya, K. (Keio Univ. Sch. Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan); Mikata, A.; Kageyama, K.; Kameya, T.; Shimamoto, Y. *Acta Pathol. Jpn.* 25(3):355-374; 1975.

A histopathological analysis of six cases (6-35 yr-old) with Castleman's tumor by light and electron microscopy is reported. All cases were hyaline-vascular type as described by Keller *et al.* As germinal center activity increased, the lymphoid follicles contained: first, lymphoid aggregation, then immature lymphoid cells, and finally were hyalinized. The lymphoid follicle was essentially similar to that of a normal lymph node undergoing some reactive process. The lesions had lymphatic sinuses around the blood vessels in the tumor parenchyma, some of which were connected to the abortive marginal sinuses. These findings and some clinical records suggest that the lesion originates from the lymph node and that its reactive hyperplasia has a role in the etiology of the lesion.

- 6410 A COMPARATIVE STUDY OF PRIMARY CELL CULTURES OF HUMAN DIFFUSE STRUMA AND THYROID CANCER. (Rus.) Demidova, S. A. (The D. I. Ivanovsky Inst. of Virology of the USSR Acad. of Medical Sciences, Moscow, U.S.S.R.); Levina, D. S.; Guschin, B. V.; Ritova, N. M.; Bljumkin, V. N.; Guschina, E. A.; Klimenko, S. M.; Nikolaev, G. I. *Vopr. Onkol.* 21(6):83-88; 1975.

Light and electron microscopic findings on cell cultures from diffuse struma and adenocarcinoma of the human thyroid gland are presented. Cells obtained from diffuse struma (nonmalignant tissue) formed a continuous monolayer consisting of monomorphous epithelioid cells with high adhesive capacity in 83 of

100 cases. Cells from thyroid adenocarcinoma formed islands with reduced adhesiveness in 5 of 7 cases. The cultures consisted of polymorphous cells. Polynucleated giant cells and cells with colorless spheroid inclusions in the nuclei were also encountered. The large, light-colored tumor cells contained no nucleoli, fully or partly intact organoids, osmiophilic inclusions and vacuoles in the cytoplasm. The scarcer small dark cells contained large quantities of filamentous structures but no organoids. Cultures from adenocarcinomas obtained from patients irradiated with 4,500-5,000 rads contained large degenerating light-colored cells surrounded by a dense collagen mass. The cytoplasm was filled with collagen in certain cases. There were no small dark cells in these cultures. Oncornavirus was not detected in irradiated or nonirradiated cells.

- 6411 EFFECT OF NEUROTRANSMITTERS, GUANOSINE TRIPHOSPHATE, AND DIVALENT IONS ON THE REGULATION OF ADENYLATE CYCLASE ACTIVITY IN MALIGNANT AND ADENOSINE CYCLIC 3':5'-MONOPHOSPHATE-INDUCED "DIFFERENTIATED" NEUROBLASTOMA CELLS. (Eng.) Prasad, K. N. (Univ. Colorado Med. Cent., Denver); Gilmer, K. N.; Sahu, S. K.; Becker, G. *Cancer Res.* 35(1):77-81; 1975.

Adenylate cyclase activity in homogenates of malignant mouse neuroblastoma (clone NBP₂) cells and cells "differentiated" by RO20-1724 (an inhibitor of cyclic AMP phosphodiesterase) was studied. Enzyme activity was 250% of the control value if 10 µg/ml prostaglandin E₁ (PGE₁) was added and 250% of the control if both PGE₁ and guanosine triphosphate (GTP) were added at that level to differentiated cells. Addition of PGE₁, with or without GTP, to malignant cells resulted in enzyme activity of about 200% of the control value. 3,4-Dihydroxyphenylethylamine (dopamine, 100 µM) added to differentiated cells gave enzyme activity 180% of the control; with malignant cells, 160% of the control value. Dopamine did not significantly change the enzyme activity of x-irradiated (600 rads) cells. CaCl₂ (3 mM) stimulated adenylate cyclase activity in both types of cells to a similar level. The K_m and V_{max} values for the two types of cells were similar. MgCl₂ and MnCl₂ at concentrations of 1 mM or more above the standard medium concentrations inhibited enzyme activity more in differentiated cells than in malignant cells. This study shows that the sensitivity of adenylate cyclase to neurotransmitters and to Mg⁺⁺ and Mn⁺⁺ increases in differentiated neuroblastoma cells; the sensitivity of PGE₁-stimulated enzyme activity to GTP also increases in these cells. The authors suggest that the reverse may be true during malignant transformation.

- 6412 ABNORMAL GROWTH PATTERNS OF THE PELVIC UROTHELIUM IN THE PRESENCE OF RENAL CALCULI. (Eng.) Iyengar, B. (Maulana Azad Medical Coll., New Delhi-110 001, India); Uma, K.; Malhotra, V.; Chandra, K. *Indian J. Cancer* 12(2):158-163; 1975.

The frequency of occurrence of metaplasia and neoplasia and stone formation were investigated. A

total of 154 nephrectomy specimens removed surgically for renal calculi were studied; many cases showed an overlapping of urothelial changes. Proliferation of the transitional epithelium with multilayering of the epithelium was found in 40 cases, and papillary formation in 16 cases. Squamous metaplasia was noted in 18 cases; a carcinomatous change occurred in six cases. Ulceration of the mucosa was seen in 45 cases. While gradual transitions were seen in cases of transitional cell carcinoma and squamous cell carcinoma, an abrupt change was noted in pyelitis cystica glandularis. Squamous metaplasia was found in two different forms, involving intercellular bridges or a gradually merging continuous layer of squamous epithelium. The metaplastic and proliferative changes were seen mostly away from areas of ulceration and inflammation. However, intense inflammatory infiltrates, including lymphocytic aggregates, plasma cells, and abscesses were seen in the areas of ulceration. Calculi were thus associated with all the types of growth abnormalities. It is postulated that the malignant potential of the urothelium is due to the varying chemical environment provided by the urine.

- 6413 ULTRASTRUCTURAL ANALYSIS OF A MASSON'S HUMID MENINGIOMA. (Fre.) Choux, R. (Laboratoire d'Anatomie pathologique et de Neuro-pathologie, Faculté de Médecine, Boulevard Jean-Moulin, F 13385 Marseille Cedex IV.); Hassoun, J.; Gambarelli, D.; Sedan, R.; Toga, M. *Bull. Cancer (Paris)* 62(2):125-136; 1975.

A case is reported of Masson's humid meningioma occurring in a 48-yr-old woman whose presenting symptom was "blacking out" with loss of the power of speech. A white, homogeneous tumor attached to the dura mater at the level of the sagittal sinus was excised and diagnosed microscopically as a meningioma. Histological study was carried out after tumor was chilled in isopentane, sliced and stained with Red O oil or by the Gomori alkaline phosphatase method. The alkaline phosphatase reaction did not reveal vascular proliferation and eliminated the diagnosis of cerebral hemangioblastoma or angioblastic meningioma. Red oil O stained only the fine cellular fibers and not the cavities they enclosed. Excess lipid was observed only in the massed interstitial histiocytes and not in the neoplastic cells. Numerous weakly osmiophilic vacuoles were visualized within the cell, indicative of cellular hypercatabolism. Another inclusion, non-lipid in nature and also numerous, was large, amorphous and surrounded by an indented or perforated double membrane. Another inclusion with a dense network, visible in the perikaryon, could represent an early stage in the formation of calcium deposits. The arachnoid origin of the tumor cells was confirmed by the presence of large tonofibrils and characteristic desmosomes. The intercellular spaces contained a loose material associated with fibers in different stages of collagen formation. These extracellular fibers appeared to intermingle with the intracytoplasmic tonofibrils. The meningiocyte might be responsible for the production of the intercellular collagen. The study confirms the single

cell origin of the meningiomas which can be explained by the double ectomesenchymatous potential of the arachnoid cell.

- 6414 VON HIPPEL-LINDAU'S DISEASE: CASE REPORT AND ONCOGENIC CONSIDERATION. (Eng.) Rho, Y.-M. (Inst. Forensic Med., New York Univ., N.Y.); Sachdev, V. P.; Malis, L. I. *Mt. Sinai J. Med. N.Y.* 42(3):245-251; 1975.

A case history of von Hippel-Lindau's disease in a 48-yr-old woman is presented. The history of the illness dated back 16 yr when the patient developed progressive difficulty in walking, slurring of speech, frequent headaches, and double vision. Suboccipital craniectomy was performed twice for excision of a cerebellar hemangioblastoma over a 10-yr period. Funduscopy revealed bilateral papilledema as well as an angiomatous lesion of the upper outer quadrant of the right retina. Bilateral retrograde brachial angiography showed a large highly vascular tumor involving the posterior fossa, replacing almost entirely the right cerebellar hemisphere and extending across the midline. The patient underwent another suboccipital craniectomy but died of massive air embolism during the operation. At autopsy, hemangioblastomas were found in the cerebellum, cervical spinal cord, and retina of the right eye. Multiple nonvasoformative cysts were seen in the pancreas, kidneys, and liver. Three nonspecific leiomyomata were noted in the uterus. The adrenal medulla was replaced by a tumor 5 cm in diameter. Microscopic examination showed a large tumor that was gradually arising out of the adrenal medulla. Except for nuclear characteristics that resembled pheochromocytoma, the cellular pattern of this tumor had a close morphologic resemblance to the hemangioblastomas of the central nervous system. The present case demonstrates the strong hereditary nature of this phacomatosis; 3 of 7 siblings were definite diagnoses and at least one more was probably affected. It is suggested that the hemangioblastomas of the central nervous system and retina, pheochromocytomas of the adrenal, paragangliomas of the sympathetic chain, and renal cell carcinomas reported in von Hippel-Lindau's disease may have a common oncogenic factor, and that these tumorous lesions may represent divergent manifestations of the same genetic defect.

- 6415 INDIVIDUAL ASPECTS OF CANCER CELLS: SPECIAL KARYOGRAPHIC TECHNIQUE. (Eng.) Wainrach, B. (Beilinson Hosp., Petah Tikva, Israel). *Isr. J. Med. Sci.* 11(4):358-366; 1975.

Cancer cells from patients with different kinds of cancer were studied by karyography in an attempt to establish a new basis for the individual approach to neoplastic diseases. Histological sections prepared from tumors fixed in 10% formalin were stained with hematoxylin and eosin. The sections were photographed at a magnification of 1,000x. Interphase nuclei of the same cancer cell line or clone were identified and the contours of interphasic nuclei of normal and cancer cells were transcribed using a special karyo-

graphic technique. The resulting waves were arranged consecutively and a characteristic undulating line was obtained. The undulations were analyzed according to their general form (regularity and position of the waves, and type and frequency of the irregularities) and their individual characteristics. The karyographic pattern of nuclei from four basal cell carcinomas revealed undulations that were irregular with differences in height and width or with the wave axis showing different angles when related to a horizontal reference line. By comparing the karyographic pattern of the tumor nuclei with that of normal basal nuclei in the same patient, an impression of the degree of malignant transformation could be obtained. An attempt was also made to correlated the karyographic irregularities seen in ten cases of poorly differentiated adenocarcinomas of the breast with the degree of malignancy. A favorable group (four patients who remained alive 11-15 yr after their first treatment) and an unfavorable group (four patients who died 0.5-4 yr after their first treatment) were compared. In the favorable group, the karyographic undulations were generally regular with similar and fairly symmetrical waves. In the unfavorable group, irregular waves, with frequent deviations of the wave axis were evident. Six of the breast tumors studied were of the monoclonal and six of the polyclonal cell type. In the group of long-term survivors, monoclonal tumors predominated whereas a polyclonal cell constitution was seen in 4 of 6 patients with an unfavorable course. Karyographic tracings of four fibrosarcomas showed a progressive disorganization of the undulations in the more malignant cases, with an accentuated variability of the waves and frequent changes in the wave axis. It is concluded that karyography in connection with other parameters such as the chromatin pattern, DNA measurements and the idiogram may permit the development of an "identity card" for each cancer cell line and may provide a lead to the biological behavior of individual tumor.

- 6416 PLASMA CELL AND MONOCYTE (MONO-MYELOCYTE) DYSCRASIAS AND THEIR SPECIFIC PROTEIN MARKERS--MONOCLONAL IMMUNOGLOBULINS AND LYSOZYME. (Eng.) Osserman, E. F. (Coll. Physicians and Surgeons, Columbia Univ., N.Y.); Farhangi, M. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 142-148.

The clinical and laboratory observations in a patient who developed mono-myelocytic leukemia (MML) as a terminal event after multiple myeloma (MM) and amyloidosis with immunoglobulin-light chains are reported. The white male patient had a history of penile and urethral warts from age 19, and at age 21 was first noted to have persistent proteinuria, intermittent fevers, and back pain. At age 23, he was diagnosed as having overt MM with wide-spread osteolytic lesions, anemia, uremia, and hypercalcemia; the bone marrow revealed 65% plasma cells, and there was 10-20 g of λ Bence-Jones (BJ) proteinuria per day. Melphalan, prednisone, and nortestost-

erone achieved only partial and short-term improvement; progressive objective and subjective improvement were achieved when cyclophosphamide was substituted for melphalan. This period of remission lasted for three years, during which time the patient was able to engage in essentially normal activities. Because of marked leukopenia and thrombocytopenia, the cyclophosphamide was discontinued, and two months later he sustained the first of a series of respiratory and urinary tract infections. He was found to be anemic, and the bone marrow showed abnormal megaloblastoid erythropoiesis, increased numbers of monocytes and monoblasts, and only 6% plasma cells. He remained markedly pancytopenic and required frequent transfusions of whole blood. There were gradual increases in peripheral blood monocytes, and the serum and urinary lysozyme levels. The final 11 mo were characterized by a succession of febrile episodes due to bacterial pneumonias, urinary tract infection cellulitis, and abscesses. Postmortem examination showed extensive infiltration of the spleen, liver, kidneys, skeletal and heart muscles, and marrow with leukemic monocytes. There were extensive condylomat of the glans penis, penile and prostatic urethra, bladder hypertrophy, and bilateral pyelonephritis. It is hoped that further elucidation of the functional interrelationships of mononuclear phagocytes and plasma cells and the pathogenic factors contributing to their respective dyscrasias will make it possible to avoid the late complication of these leukemias in successfully treated cases of MM.

- 6417 MUCOUS SECRETION IN RAT COLONIC MUCOSA DURING CARCINOGENESIS INDUCED BY DIMETHYLHYDRAZINE: A MORPHOLOGICAL AND HISTOCHEMICAL STUDY. (Eng.) Filipe, M. I. (Westminster Medical Sch., London SW1P 2PP, England). *Br. J. Cancer* 32(1): 60-77; 1975.

The morphological and mucin changes occurring in the colonic epithelium of 1,2-dimethylhydrazine-2HCl-treated (DMH, 20 mg/kg/wk, sc) female Wistar rats were studied. The experiment lasted for 29 wk, and the colonic tissues were examined histologically at weekly intervals. The first macroscopic changes were seen as small excrescences in the transitory distal-proximal colon at 13 wk. The number and size of these lesions increased with the length of DMH exposure. Of the 54 lesions found between weeks 19-28, 29 were identified as invasive carcinomas. The earliest histological changes were foci of hyperplasia and mild-severe dysplasia occurring during weeks 3-6; lesions of this nature increased in number and severity to week 13. From the 13th wk, the number of focal areas showing severe dysplasia increased markedly, and histological features of carcinoma *in situ* appeared. Invasive carcinoma first appeared after 19 injections of DMH; invasive tumors were found in all but one rat treated for longer than 19 wk. All carcinomas in the distal colon were well-differentiated adenocarcinomas, whereas two of the invasive tumors in the proximal colon presented features of "signet ring" carcinomas. DMH treatment produced changes in the mucin composition consisting of a predomi-

nance of sialomucins in the goblet cells, accompanied by a decrease in or absence of sulfomucins. No alteration in mucin composition was noted during the first six weeks, but between the weeks 7-18, changes were observed in the areas of mild to moderate dysplasia. Changes in mucin composition were more frequently encountered after week 28. These findings correlated well with those observed in human colonic carcinoma, and supported the hypothesis that mucin changes characterized by an increase in sialomucins might reflect early malignant transformation.

6418 STABILITY OF X CHROMOSOMAL INACTIVATION IN HUMAN SOMATIC CELLS TRANSFORMED BY SV-40. (Eng.) Romeo, G. (International Inst. Genetics and Biophysics, Via Marconi, 10, I-80125 Naples, Italy); Migeon, B. R. *Humangenetik* 29(2):165-170; 1975.

The relationship between the glucose-6-phosphate dehydrogenase (G6PD) and sex chromatic phenotypes of cells undergoing malignant transformation is elucidated. Clones of human fibroblasts heterozygous for the G6PD variants were infected with SV-40 virus. Transformed cells from nonclonal populations of fibroblasts heterozygous for G6PD and hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) deficiency were screened. The colonies from these cells that expressed a single G6PD type also had the HGPRT phenotype. No G6PD heteropolymer synthesis by these colonies was detected. The incidence of sex chromatin was significantly less in the cells after transformation and the transformed cells were aneuploid. It is likely that the loss of sex chromatin reflects the loss of the inactive X chromosome soon after transformation. This study confirms earlier reports that X inactivation is stable in human somatic cells.

6419 A MODEL FOR LYMPHATIC METASTASIS AFTER INTRADERMAL INOCULATION OF TUMOUR CELLS. (Ger.) Wohlrabe, K. (Zentralinstitut für Mikrobiologie und experimentelle Therapie DDR-69 Jena, Beutenbergstr. 11, East Germany). *Arch. Geschwulstforsch.* 45(2):131-135; 1975.

A simple and reliable *in vivo* model for testing the inhibiting effect of cancerostatics on tumor growth and lymphatic metastasis is described. Male and female ABAF₁ mice were inoculated with Ehrlich ascites carcinoma cells (2 x 10⁶ cells/20 µl, id) 1 cm below the tail root. Tumors appeared at the injection site within 10-12 days in all animals. Lymphatic metastasis occurred to the inguinal, abdominal, para-aortal, and axillary lymph nodes. The inhibition of tumor growth by cancerostatics was tested from the fifth day onward, and the inhibition of the metastasis was studied under the same therapy instituted on the 19th day after tumor implantation. The effect of the cancerostatics was evaluated by comparison of the fresh weight of tissues in treated and untreated animals.

6420 CYTOCHEMICAL STUDY OF SECRETORY PROCESS IN TRANSPLANTABLE INSULINOMA OF SYRIAN GOLDEN HAMSTER. (Eng.) Novikoff, A. B. (Albert Einstein Coll. Medicine, Yeshiva Univ., Bronx, N.Y. 10461); Yam, A.; Novikoff, P. M. *Proc. Natl. Acad. Sci. U.S.A.* 72(11):4501-4505; 1975.

Transplantable insulinomas in Syrian golden hamsters were examined to elucidate the secretory process in these cells. The tumors were excised 18-24 days after sc inoculation. Electron microscopy, including phosphatase cytochemistry, indicated that the secretory granules of a proinsulin- and insulin-producing insulinoma are packaged by a special region of the endoplasmic reticulum designated GERL (Golgi Endoplasmic Reticulum, Lysosomes) because of the spatial relationship of this region to the Golgi apparatus and its apparent role in producing lysosomes. The granules are not derived from the Golgi apparatus. Because of preliminary evidence of enzymatic similarity, it is suggested that these observations may also be true of normal pancreatic β-cells.

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6468 KAPOSI'S SARCOMA. REPORT OF TWO CASES. (Jpn.) Tomino, Y. (Sapporo Municipal General Hosp., Sapporo, Japan); Noro, T.; Yoshiki, T.; Shirai, T.; Itoh, T. *Gan No Rinsho* 21(13):1217-1222; 1975.

6469 KAPOSI SARCOMA IN A RENAL TRANSPLANT RECIPIENT. (Eng.) Straehley, C. J., III (Penrose Hosp., 2215 N. Cascade Ave., Colorado Springs, Colo., 80907); Santos, J. I.; Downey, D. M.; Lewin, K. J. *Arch. Pathol.* 99(11):611-613; 1975.

6470 SUBCUTANEOUS LIPOSARCOMA OF SCAPULAR AREA. (Eng.) Meyer, K. K. (No affiliation given); Kelly, J. A.; Rockman, M. *Guthrie Bull.* 44(3):141-146; 1975.

6471 DIFFERENTIAL INDUCTION OF CHROMOSOME ABERRATIONS IN MAMMALIAN CELL LINES. (Eng.) Scott, D. (Christie Hosp., Withington, England); Fox, M.; Fox, B. W. *Mutat. Res.* 29(2):201-202; 1975.

6472 ANGIOIMMUNOBLASTIC LYMPHADENOPATHY: REPORT OF ONE CASE. (Spa.) Giralt, M. (Servicio Regional de Hematologia, Ciudad Sanitaria de la Seguridad Social, Avenida Isabel la Catolica, 5, Zaragoza, Spain); Pardo, J.; Vazquez Arnedo, M.; Garcia Julian, G.; Raichs, A.* *Sangre (BARC)* 20(2):218-224; 1975.

6473 IMMUNOBLASTIC SARCOMA WITH AUTO-IMMUNE MANIFESTATIONS. (Fre.) Schaeffer, A. (Policlinique Hopital Henri Mondor, 51, avenue du Marechal de Lattre de Tassigny, F 94010 Creteil, France); Lejonc, J.-L.; Reyes, F.; Kalifat, S.-R.; Tulliez, M.; Sultan, C.; Portos, J.-L. *Ann. Med. Interne (Paris)* 126(5):355-360; 1975.

6474 LEIOMYOSARCOMA OF THE LONG SAPHENOUS VEIN. (Eng.) Jernstrom, P. (California Hosp. Med. Cent., 1414 South Hope St., Los Angeles); Gowdy, R. A. *Am. J. Clin. Pathol.* 63(1):25-31; 1975.

6475 ALVEOLAR RHABDOMYOSARCOMA OF THE ETHMOID SINUS. (Eng.) Makishima, K. (Univ. Pennsylvania Sch. Med., Philadelphia, Pa.); Iwasaki, H.; Horie, A. *Laryngoscope* 85(2):400-410; 1975.

6476 LYMPHANGIOSARCOMA ARISING IN CONGENITAL LYMPHEDEMA. (Eng.) Laskas, J. J., Jr. (Univ. Pennsylvania Sch. Med., Philadelphia, Pa.); Shelley, W. B.; Wood, M. G. *Arch. Dermatol.* 111(1):86-89; 1975.

6477 HISTOPATHOLOGICAL AND ULTRASTRUCTURAL STUDY OF TUMORS INDUCED BY MURINE SARCOMA VIRUS (MSV). (Ita.) Pennelli, N. (Istituto di Anatomia Patologica I e II Cattedra, Universita di Padova, Padova, Italy); Chieco-Bianchi, L.; Collavo, D.; Cecchetto, A. *Tumori* 61(2):129-150; 1975.

6478 FIFTEEN CASES OF PHACOMATOSIS. (Fre.) Toudic, L. (Service de Pediatrie, C.H.R., 29200 Morvan-Brest, France); Masse, R.; Hery, B.; Renard, G.; Le Fur, J. M.; Castel, Y. *J. Genet. Hum.* 23(Suppl.):235-237; 1975.

6479 RECKLINGHAUSEN'S DISEASE: A GENETIC AND CLINICAL-PATHOLOGICAL STUDY WITH RESPECT TO 67 GENEALOGIES. (Fre.) Robert, J. M. (Hotel-Dieu, 1, place de l-Hopital, 69288 Lyon Cedex 1, France); Trouillas, P.; Martini, L. *J. Genet. Hum.* 23(Suppl.):231-233; 1975.

6480 MONOCYTE FUNCTION IN CHRONIC BENIGN NEUTROPENIA. (Eng.) Kay, A. B. (Royal Infirmary Edinburgh, Edinburgh EH3 9HB, Scotland); White, A. (Barclay, G. R.; Darg, C.; Raeburn, J. A.; Uttley, W. S.; McCrae, W. M.; Innes, E. M. *Lancet* 1(7903):391; 1975.

6481 INFLUENCE OF THE VIRUS OF NUCLEAR POLYHEDRUS OF *GALLERIA MELLONELLA* AND ITS DNA ON THE CHROMOSOMES OF MAMMALIAN CELLS. (Ukr.) Buzhievskiy, T. I. (Inst. Molecular Biology and Genetics, Acad. Sciences, Ukrainian S.S.R., Kiev, U.S.S.R.); Nikonenko, V. U.; Vavilina, I. V. *Dopov. Akad. Nauk. U.S.S.R. Ser. B* (3):249-252; 1975.

6482 ON MALIGNANT GIANT CELL SYNOVIOMAS. (Rus.) Rukavishnikova, V. G. (Central Res. Inst. Roentgenoradiology, U.S.S.R. Ministry Health, Moscow, U.S.S.R.). *Vopr. Onkol.* 21(7):37-43; 1975.

6483 MALIGNANT SYNOVIOMA. (Pol.) Kortas, I.
(Instytut Chirurgii PAM. I Klinika Chirurgii Ogólnej. ul. Unii Iubelskiej 1. 71-344 Szczecin, Poland); Chojnacki, J. *Wiad. Lek.* 28(7):589-592; 1975.

6484 ULTRASTRUCTURE OF ENDOMETRIAL STROMAL SARCOMA. (Eng.) Akhtar, M. (Albert Einstein Med. Cent., Philadelphia, Pa.); Kim, P. Y.; Young, I. *Cancer* 35(2):406-412; 1975.

6485 LIPOMA OF THE BROWN ADIPOSE TISSUE. (Ger.) Schwesinger, G. (Inst. Pathol, Ernst-Moritz-Arndt-Univ., Greifswald, East Germany). *Anat. Anz.* 137(5):434-439; 1975.

See also:

- * (Rev): 6002, 6004, 6005, 6006, 6027, 6028, 6031, 6036, 6037, 6048, 6054, 6055, 6060, 6061, 6062, 6063, 6064
- * (Chem): 6105, 6139, 6140, 6141, 6161
- * (Viral): 6224, 6227, 6272
- * (Immun): 6289, 6299, 6304, 6334, 6354, 6362, 6376, 6380
- * (Epid-Biom): 6486, 6500, 6501, 6509, 6584

- 6486 CARCINOMA OF THE GLOTTIC LARYNX. (Eng.)
Daly, C. J. (1275 York Ave., New York,
N.Y. 10021); Strong*, E. W. *Am. J. Surg.* 130(4):
489-492; 1975.

A retrospective study of 521 patients treated for histologically proved squamous cell cancer of the glottic larynx was presented. The patients were predominantly male (93%), of average age 61 yr. No prior treatment had been administered to 89.2% of the cases studied, while 10.2% had previous operation and/or radiation. Only 4.7% of the patients were nonsmokers, while 9% were nondrinkers and 36% "social" drinkers. In 88%, the initial symptom was a change in voice quality; laryngeal pain, hemoptysis, dysphagia, and respiratory obstruction were signs of advanced disease. Synchronous or metachronous second primary lesions occurred in 14.5%; the second primary occurred in the head and neck, lung, gastrointestinal tract, and genitourinary system. The lesion was confined to the true vocal cord in 55% of the patients studied, involved the ventricle and/or ventricular band in 21%, and had subglottic extension in 22%. Eleven patients received therapy, and 454 were treated surgically. Surgical procedures included endoscopic cordectomy or vocal and stripping (2%), partial laryngectomy (55%), total laryngectomy (38%), and wide field laryngectomy (5%) in the primary patients; the majority of the secondary patients (57%) underwent total laryngectomy. The 104 unilateral and bilateral radical neck dissections performed revealed histologically positive lymph nodes in 51% in the primary group and 67% in the secondary group. The most frequent complications were fistula formation, pharyngocutaneous fistula, microstomia, wound infection, gastrointestinal hemorrhage, and loss of voice; 83% were able to use esophageal speech. Lesions recurred in the larynx and distant metastases developed. The determinant five and 10 year survival rates for primary patients were 81.5% and 80% respectively, while the previously treated patients had a much worse prognosis.

- 6487 MARITAL AND REPRODUCTIVE EXPERIENCE IN A
COMMUNITY-WIDE EPIDEMIOLOGICAL STUDY OF
BREAST CANCER. (Eng.) Lilienfeld, A. M. (Johns
Hopkins Sch. Hygiene and Public Health, 615 N. Wolfe
St., Baltimore, Md. 21205); Coombs, J.; Bross, I. D.
J.; Chamberlain, A. *Johns Hopkins Med. J.* 136(4):
157-162; 1975.

The relationship of marital and reproductive experience to human breast cancer was studied using data collected during 1956-1962. Information was obtained from all women with cancers of the reproductive organs in the Buffalo, New York area. A probability sample of the same population was selected. The analysis of marital and reproductive histories in the Buffalo population study confirms previous reports of an increasing risk of breast cancer with increasing age at first parturition. Attempts to distinguish the two interpretations mentioned by analyzing the interval between first marriage and time of birth in addition to age at first parturition were not conclusive. This necessitated a similar analysis of data available in a larger series of 1164 breast cancer

patients and 1200 nonneoplastic controls hospitalized during 1957-1965. The results do not show an influence of interval between first marriage and first parturition but do show an increased risk of breast cancer with increasing age at first parturition. In a series of 103 patients under 40 yr of age with breast cancer and 101 nonneoplastic controls, the relative risk (compared to that of nonparous women = 1.00) for women < 20 yr at first parturition was 0.57; for those over 30 yr, 2.75. For those experiencing first parturition at 25-29 yr and more than 2 yr after first marriage, the relative risk was 3.27. These comparisons involved small numbers of women. The results are thus consistent with a protective effect of an early age at first parturition.

- 6488 EPIDEMIOLOGICAL CANCER RESEARCH. (Fin.)
Saxen, E. (Suomen Syöpärekisteri, Liisan-
katu 21 B, 00170 Helsinki 17, Finland); Hakama, M.;
Teppo, L. *Duodecim* 90(22):1597-1604; 1974.

A study was made of the fact that the incidence of lung cancer in Finland was five times higher than in Norway. Thirty-two Finnish and 10 Norwegian public health nurses acted as the interviewers for 10,000 men. Interviews were conducted in six areas in both countries, chosen to represent high, normal, and low lung cancer risk areas in cities and rural areas. The results demonstrated that Norwegians begin smoking at an earlier age than Finns, and that a greater number of Norwegians are still currently smoking. The number of lung cancer cases in Finland was higher in all study areas than could have been estimated on the basis of cigarette consumption. In Finland, smoking has a long tradition, whereas in Norway the habit is relatively recent. The incidence of lung cancer and the amount of cigarette consumption were measured for the same span of time. Since the development of lung cancer presupposes a long period of exposure, there should have been an interval of several years, maybe decades between the smoking habit interviews and the measurement of lung cancer incidence. Therefore, quantitatively the strength of the correlation could not be measured.

- 6489 CHILDHOOD CANCER IN FINLAND 1953-1970.
(Fin.) Salonen, T. (Helsingin yliopiston
III patologistian laitos, 00290 Helsinki 29, Finland);
Hakulinen, T.; Teppo, L. *Duodecim* 90(21):1449-1459;
1974.

Data involving 2,605 children (1,440 boys and 1,165 girls) under 15 yr of age with malignant tumors, who were reported to the Finnish Cancer Registry during 1953 to 1970 were evaluated. Diagnosis was based on histological or cytological examination; in 6% of the cases the information was obtained at autopsy. Boys had a consistently higher incidence of tumors than girls. Incidence peak for embryonal tumors (e.g. neuroblastomas, retinoblastomas, and neuroblastomas) was in the less than one yr age group. With bone tumors and Hodgkins disease the incidence increased toward puberty. The incidence peak for

leukemia and brain tumors occurred in the one to four yr-age group. The incidence of soft tissue sarcomas decreased up to the tenth yr of age and then increased again. From 1950 to 1970, the tumor incidence in children under one yr of age increased. If, after allowing for improved diagnostic methods and registry, there is an increase in tumor incidence in children under one yr of age, this could be an indication that the environment, possibly even intrauterine, contains an increasing number of carcinogens. There was no significant increase in the incidence for older children.

6490 CHARACTERIZATION OF PROSTATIC CARCINOMA AMONG BLACKS: A PRELIMINARY REPORT.

(Eng.) Jackson, M. A. (Howard Univ. Coll. Medicine, Washington D. C. 20059); Ahluwalia, B. S.; Attah, E. B.; Connolly, C. A.; Herson, J.; Heshmat, M. Y.; Jackson, A. G.; Jones, G. W.; Kapoor, S. K.; Kennedy, J.; Kovi, J.; Lucas, A. O.; Nkposong, E. O.; Olisa, E.; Williams, A. O. *Cancer Chemother. Rep. (Part 1)* 59(1):3-15; 1975.

A study was designed to compare United States (Washington, D. C.) black prostatic carcinoma patients (high-risk group) with Nigerian (Ibadan) black prostatic carcinoma patients (low-risk group). Although the material is meager, preliminary analyses suggested that carcinoma of the prostate is a common disease in both US black men (196 of 1,000 autopsies) and in Nigerian black men (67 of 1,000 autopsies). The tumor tended to be of a higher histologic grade (less well differentiated), and the carcinomatous foci were more numerous in the Nigerian patients. Fifty-three percent of US patients were in stages I and II when the disease was first discovered. Plasma testosterone, estrone, and estradiol concentrations did not differ significantly between US patients and controls. A statistically significant positive association was indicated between carcinoma of the prostate and the following epidemiologic variables: racial admixture, age of puberty, and age of first coitus. The median age of necropsy cases with carcinoma was 50.0 yr in Nigeria and 68.3 yr in the US.

6491 PROSPECTIVE STUDIES ON CANCER EPIDEMIOLOGY BASED ON CENSUS POPULATION IN JAPAN.

(Eng.) Hirayama, T. (Natl. Cancer Center, Res. Inst., Tokyo, Japan). *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 26-35.

Findings are reported from the first 8 yr of a prospective study involving 265,118 adults on the health consequences of selected risk factors. Deaths from cancer were categorized according to the types of tumor involved. Cigarette smoking was found to increase the risk of death from cancer more than any of the other habits studied. The risk was directly related to the number of cigarettes smoked each day. Individuals who had stopped

smoking for 10 yr or longer had an almost similar risk of death from all causes and cancer at all sites as nonsmokers. The daily consumption of alcohol significantly increased the risk of cancers of the thyroid, mouth, mediastinum, esophagus, and lung. Regular drinking of alcohol appreciably stimulated the risk of lung cancer for nonsmokers; however, it did not increase the already-enhanced risk of this cancer for smokers. The combined habits of daily alcohol drinking and daily smoking of 20 or more cigarettes enhanced the risk of the following diseases: subarachnoid hemorrhage, liver cirrhosis, and cancers of the mouth, esophagus, and liver. The daily consumption of 360 ml of milk significantly reduced cancer of the stomach, and daily consumption of green vegetables reduced the incidence of cancers of the esophagus, mediastinum, and prostate. Daily intake of meat increased the risk of cancers of the liver, pancreas, lung, and mediastinum. Fish consumption increased the risk of cancers of the stomach, rectum, and urinary bladder, and daily hot green tea enhanced the risk of cancers of the mouth, esophagus, stomach, and mediastinum, and of lymphomas and Hodgkin's disease. Child-bearing reduced the risk of cancers of the breast, rectum, lung, and ovaries. This survey provides the opportunity to examine the relation of known or suspected risk factors to death rates in a population with genetic, environmental, and cultural differences from Western populations.

6492 INCIDENCE, MORTALITY, AND PREVALENCE AS INDICATORS OF THE CANCER PROBLEM. (Fin.)

Teppo, L. (Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland); Hakama, M.; Hakulinen, T.; Saxen, E. *Duodecim* 90(22):1541-1547; 1974.

New cancer cases in the Finnish Cancer Registry from 1953 to 1970 were studied. The following information was known in each case: the primary location of the tumor, time of determination and whether the patient was still alive at the end of 1970. The incidence (new cancer cases) and mortality were clearly higher among men due to the poor prognosis associated with lung cancer cases. The prevalence (total number of cancer cases) was higher with women because of the relatively long average life span of genital and breast cancer patients. Of all cancers in men, 13% were of the stomach, 8.9% prostate, 4.1% pancreas, 3.9% bladder, 3.1% intestine, 3.1% colon, 3.0% leukemia, 2.9% larynx, 2.9% lymphomas, 2.5% kidney, 2.4% lip, 1.9% esophagus, and 17% other tumors. In women 19.6% were breast cancers, 12.2% stomach, 6.6% cervical, 6.3% uterine, 6.0% ovarian, 5.3% intestinal, 4.0% colon, 3.8% pancreas, 3.0% lung, 2.7% leukemia, 2.4% kidney, 2.2% esophagus, 1.7% lymphomas and 24.5% other tumors. The highest incidence was in the 80 to 84 yr-age group. Mortality and prevalence figures are always behind the incidence figures and are, therefore, slower as indicators of changes in general trends. Incidence and mortality figures are more important in studying the etiology and the possibility of early prevention of a disease, while prevalence figures are quite useful, in addition to the incidence and mortality figures for developing a health care organization.

- 6493 A FOLLOW UP STUDY OF ORAL CANCER AND PRECANCEROUS LESIONS IN 57,518 INDUSTRIAL WORKERS OF GUJARAT INDIA. (Eng.) Bhargava, K. (Government Dental Coll. and Hosp., Ahmedabad-380 016 India); Smith, L. W.; Mani, N. J.; Silverman, S., Jr.; Malaowalla, A. M.; Bilimoria, K. F. *Indian J. Cancer* 12(2):124-129; 1975.

Of the 57,518 persons examined in a four-year investigation of oral cancer and precancerous lesions among industrial workers of Gujarat, 43,654 were re-examined two years later. The rates of incidence and disappearance of various precancerous lesions were studied in relation to personal characteristics and habits. Although the incidence of new lesions was high (11,905), regression rates were also high for nicotine stomatitis, leukoedema, submucous fibrosis, and lichen planus. Of the 22 new cases of histologically confirmed oral cancer, 13 developed as new lesions and nine through transformation of pre-existing lesions. Except for leukoplakia, which had a malignant transformation rate of 0.13%, no other lesions classified as precancerous developed into cancer. Tobacco smoking, alone or in combination with other factors such as pan/supari chewing, was the most significant factor in the development of lesions. This was particularly true for nicotine stomatitis, leukoedema, and cancer. The two-year incidence rate of oral cancer was 50.5/100,000 population.

- 6494 MULTIPLE STUDY APPROACHES (FOR CANCER) TO A WELL DEFINED POPULATION OF PARSIS. (Eng.) Gangadharan, P. (Tata Memorial Hosp., Parel, Bombay, India); Jussawalla, D. J.; Rao, D. N.; Paymaster, J. C. *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 18-25.

A retrospective study of the organ-specific incidence of cancer in Parsi and non-Parsi subjects was made from an analysis of records of the Tata Memorial Hospital (1957 to 1965) and of the Bombay Cancer Registry (1964 to 1966). The Parsis of Greater Bombay form a closely-knit and highly-inbred community. The socioeconomic conditions of the Parsis tend to be better than those of other social groups, and their diet and living habits are similar to those of Western populations. Most refrain from smoking and from chewing pan-tobacco. Correspondingly, only 23% of the total cancers in Parsi patients at the Tata Memorial Hospital were oral or pharyngeal tumors, as compared to 49% for non-Parsis. The age-adjusted incidence rate for all forms of cancer in Parsis was lower than that in the total population of Greater Bombay; the rates for Parsi men and women were 96 and 115 per 100,000 population, respectively, compared to 139.5 and 131.1 for non-Parsis, respectively. The age-adjusted incidence rates revealed a greater incidence of certain types of cancer in the Parsis as compared to the general population; breast cancer among Parsis was found to display an incidence 1.7 times higher than in non-Parsis. A

prospective study of Parsi and non-Parsi women is now underway to investigate the possibility of a viral etiology for breast cancer. The possible involvement of cystic diseases in the development of malignancy is also to be assessed.

- 6495 BLOOD-VESSEL NEOPLASMS IN CHILDREN: EPIDEMIOLOGIC ASPECTS. (Eng.) Chabalko, J. J. (Natl. Cancer Inst., Bethesda, Md. 20014); Fraumeni*, J. F., Jr. *Med. Pediatr. Oncol.* 1(2):135-141; 1975.

In a search for etiologic leads to blood-vessel neoplasms, 111 death certificates of U.S. children who died between 1960 and 1968 of angiosarcoma, hemangioendothelioma, and hemangiopericytoma and 127 medical records of similar cases from 12 institutes were examined. The available data provided no leads to environmental agents (vinyl chloride, thorotrast, arsenic) that could produce vascular liver tumors in adults; however one infant, who died from a hepatic tumor, lived within a mile of an industrial source of polyvinyl chloride. About half of the children with hepatic hemangioendotheliomas had associated skin hemangiomas, which may aid in the differential diagnosis of liver tumors in infancy. Hepatic hemangioendotheliomas also predominated in girls, a possible clue to the origin of the tumor. A familial influence was suggested by one sibling aggregation of cutaneous hemangioendotheliomas.

- 6496 VALUE OF THE DETERMINATION OF HYDROXY-5 TRYPTOPHAN AND OF HYDROXYINDOLES IN BIOLOGICAL MEDIA IN THE COURSE OF CARCINOIDOSIS. (Fre.) Bousquet, B. (UER de Biologie Humaine et Experimentale, Universite Rene-Descartes, Paris, France); Dreux, C.; Girard, M.-L. *C. R. Acad. Sci. [D] (Paris)* 280(8): 1043-1046; 1975.

Chromatography and spectrofluorimetry were used to identify the precursor metabolite of serotonin hydroxy-5 tryptamine (5 HT), hydroxy-5 tryptophan (5 HTP) and hydroxyindoles; to determine normal reference values; and to examine certain pathological conditions, especially those caused by carcinoid tumors. Reference values for 5 HTP were determined from urine samples of normal subjects and from 12 patients with carcinoid tumors. Values were also determined for blood and urinary serotonin and urinary hydroxy-5 indole acetic acid (5 HIA). There was no correlation between the rate of urinary 5 HTP and that of other indole derivatives eliminated in the same way; in five cases, 5 HTP was normal whereas 5 HT and 5 HIA were increased. However, in seven other cases, the rate of 5 HTP was clearly above normal and seemed to be related to a significant serotoninuria. A case of metastasized bronchial carcinoma demonstrated extremely high rates for urinary 5 HTP and 5 HT, whereas 5 HIA was below normal. These results confirm the generally accepted view that the urinary elimination of 5 HTP is exceptional and characteristic of a major deficit in 5 HTP decarboxylase.

- 6497 ASBESTOS MEASUREMENTS IN AMBIENT AIR.
(Eng.) Spurny, K. R. (Inst. Aerobiology, Fraunhofer-Soc., 5949 Graftschaff, West Germany); Stober, W. *Clean Air (Heidelberg, Aust.)* 9(2):38-41; 1975.

In order to establish a simple, sensitive technique for detecting airborne asbestos, four different types of filters were compared. The filters, including cellulose ester membrane filters (0.8 μ m pore diameter), silver membrane filters (0.8 μ m pore diameter), golden membrane filters (0.8 μ m pore diameter) and Nucleopore filters (different pore sizes), were exposed to samples of ambient air and clouds of asbestos fibers in laboratory chambers. They were then examined by transmission electron microscopy, light and scanning electron microscopy. The best results were obtained with the Nucleopore filters in combination with transmission or scanning electron microscopy, although magnification with the optical microscope was satisfactory. In ambient air, the efficiency coefficient of Nucleopore filters for asbestos fibers was 95-98%. Electron microprobe analysis of single fibers on the Nucleopore filter permitted chemical analysis establishing proof of the asbestos nature of the particle. An automated method for detecting and analyzing asbestos fibers in samples of ambient air is suggested.

- 6498 PRACTICAL LIMITATIONS OF CRITERIA FOR LIMITING RADIATION RISKS TO THE PUBLIC.
(Eng.) Macdonald, H. F. (Central Electricity Generating Board, Berkeley Nuclear Lab., Berkeley, Gloucestershire, GL13 9PB England). *Ann. Nucl. Energy* 2(9/10):625-635; 1975.

A sequel to a previous study, which reviewed the formal basis of the radiological protection criteria and dose limits employed in the control of radiation risks to members of the public, is presented. Methods have been employed to relate basic dose limits to measurable environmental parameters through "Derived Working Limits" (DWLs) and "Emergency Reference Levels" (ERLs). Although these parameters will continue to be relevant in cases where a single radionuclide irradiates a single organ *via* a well define pathway, the simplifications involved in their derivation limit their usefulness in many practical situations. This will become increasingly true within an expanding nuclear power industry, where a wide range of radionuclides are generated and may be released to the environment either through routine operational discharges or accidentally. As the number and types of nuclear installations grow, it will become increasingly difficult to identify unambiguously a single critical route to man, either due to variations in the isotopic mixture originating from a given source or due to the introduction of additional sources which contribute to the exposure of a given individual. While the use of DWLs and ERLs enables the operator to comply with the basic dose limits, these parameters in themselves do not provide a measure of the associated risks to the public. Dose estimation techniques, based on improved environmental

and metabolic models, are however becoming available which enable a comprehensive description to be given of the dose distribution within an individual or group for any exposure regime of interest. The implications of these new techniques in the design and operation of nuclear plants are discussed and, in the case of accidental discharge limits, a modification of the current ERL dose limits used within the U.K. is suggested to take account of the relative risks associated with single organ and whole body exposure.

- 6499 SEROEPIDEMIOLOGY OF HUMAN PAPOVAVIRUSES: DISCOVERY OF VIRGIN POPULATIONS AND SOME UNUSUAL PATTERNS OF ANTIBODY PREVALENCE AMONG REMOTE PEOPLES OF THE WORLD. (Eng.) Brown, P. (Natl. Inst. Neurological and Communicative Disorders and Stroke, Bethesda, Md. 20014); Tsai, T.; Gajdusek, D. C. *Am. J. Epidemiol.* 102(4):331-340; 1975.

A total of 1,544 sera from 28 diverse and mainly isolated populations were examined for H1 antibody to BK virus. A few isolated populations were found with negligible or absent exposure to the virus, but in most populations, antibody appeared in increasing prevalence during early childhood and remained stable throughout adult life. Antibody acquisition and prevalence rates in individual families reflected that of the general population. Examined for H1 antibody to JC virus were 393 sera from 9 of the 28 populations. Age acquisition and prevalence rates of antibody were similar to those of BK virus, but experience with the two viruses was found to occur independently in several population groups, i.e., high exposure to BK with low exposure to JC, or vice-versa. Examined for neutralizing antibody to simian virus 40 (SV40) were 151 sera with and without BK H1 antibody in individuals from several primitive populations. SV40 antibody, mainly in low titer, occurred in 35% of the BK-positive group, but only 5% of the BK-negative group, suggesting that infection with BK or a closely related virus is responsible for antibody directed against SV40 in most humans unexposed to known vaccine or monkey sources of SV40 infection.

- 6500 "INCUBATION PERIOD" IN HODGKIN'S DISEASE. (Eng.) Wagener, D. J. T. (University Hosp. St. Radboud, Nijmegen, The Netherlands); Haanen, C. *Lancet* 2(7938):747-748; 1975.

Two clusters of patients with Hodgkin's disease are described. The first cluster involved a 20-yr-old girl (index case) with stage IIIB disease and her 50-yr-old mother-in-law who developed stage IIB disease. The interval between the first possible contact of the index case and time of onset of disease in the mother-in-law was six months at the most. The second cluster included a 37-yr-old man (index case) with stage IVB disease, his 37-yr-old sister-in-law with stage IVB disease, and the latter's 26-yr-old sister-in-law with

stage IA disease. There was a two-month interval between the first contact of the index case with his sister-in-law and the appearance of symptoms in the latter. The interval between contact and onset of disease in the younger woman was difficult to determine but also appeared to be short. The patient visited her sister-in-law during the acute phase of the disease in January, 1975 and noted the first symptom of Hodgkin's disease the following March. The incubation periods observed in these clusters are shorter than previously reported and may reflect the fact that the probands in both clusters had an active disseminated form of the disease at diagnosis.

- 6501 CYTOGENETIC INVESTIGATION IN A BRAZILIAN POPULATION LIVING IN AN AREA OF HIGH NATURAL RADIOACTIVITY. (Eng.) Barcinski, M. A. (Inst. Biophysics, Centro de Ciencias Medicas, Bloco G, Cidade Universitaria, ZC-32, Rio de Janeiro, GB, Brazil); Abreu, M. do C. A.; Almeida, J. C. C. de; Naya, J. M.; Fonseca, L. G.; Castro, L. E. *Am. J. Hum. Genet.* 27(6):802-806; 1975.

Colchicine-treated lymphocytes from residents of the village of Guarapari were examined for evidence of chromosomal aberrations. Black sand in the vicinity of village contains high levels of thorium and uranium ores, and the population is exposed to external doses of radiation 10-100 times the normal background level (i.e. 640 mR/yr). A significantly greater number of chromosomal breaks was scored for cells from inhabitants of Guarapari (1.30/100 cells) than for cells from inhabitants of a control village with normal levels of radiation (0.98/100 cells). Frequencies of one-break chromosomal deletions were 1.00/100 Guarapari, 0.85/100 (control), of two-break dicentric formation 0.11/100 (Guarapari), 0.06/100 (control), and of two-break ring formation 0.03/100 (Guarapari), 0/100 (control). The higher incidence of two-hit type aberrations in the cells of Guarapari origin suggested the existence of internally-deposited sources of high linear energy transfer radiation emitters, which would be expected to induce these complex types of aberrations more efficiently than external radiation sources. However, attempts to detect above-normal body burdens of long-lived radionuclides were entirely negative. It is hypothesized that the inhabitants of Guarapari may carry body burdens of short-lived radionuclides from the inhalation of thoron and thoron daughters and that internal radiation from these sources may be responsible for much of the observed damage to chromosomes.

- 6502 A RISK AND COST EFFECTIVENESS ANALYSIS OF UNITED STATES GUIDELINES RELATIVE TO RADIOACTIVITY IN FOODS. (Eng.) Shleien, B. (Bur. Radiol. Health, Food Drug Adm., Rockville, Md.). *Health Phys.* 29(2):307-312; 1975.

The guidance for radiation risks established by the Federal Radiation Council was updated and applied to monitoring radioactivity in food. Radiation risks were estimated from data on A-bomb survivors

of Hiroshima and Nagasaki, from data on patients with ankylosing spondylitis who had received x-ray therapy, and from data on groups occupationally exposed to radiation. Radiation risks are expressed in terms of deaths per person-rem and compared to the societal risks of disease, motor vehicle accidents, and natural disasters. Risk and cost effectiveness analysis was applied to evaluate the Federal Radiation Council's guidelines concerning radioactivity in milk. The cost, or health savings to society, in terms of rem was equated with the market cost of the condemned product plus the cost of replacement. The estimated risk of death due to thyroid cancer, equivalent to the numerical dose limit for iodine-131 intake (0.000015/person/year) was three times greater than that associated with the normal occurrence of the disease (0.0000045/person/yr). Therefore, the level at which it would be economically justifiable to condemn the milk was lower than the Council's present iodine-131 level. Cost effectiveness analysis provides one approach which is useful in evaluating the present radiation guidance relative to radionuclides in foods.

- 6503 ON THE EPIDEMIOLOGY OF BRONCHIAL CARCINOMA IN THE COUNTY OF NEUBRANDENBURG. (Ger.) Schubert, A. (Hygiene-Institut, 208 Neutrelitz, Bernhard-Gorings-Str. 19, East Germany). *Z. Gesamte Hyg.* 21(3):232-234; 1975.

- 6504 CARCINOMA OF THE BRONCHUS IN DAR ES SALAAM. (Eng.) Speight, A. N. P. (Univ. Dar es Salaam, Tanzania). *East Afr. Med. J.* 51(12):903-908; 1974.

- 6505 OESOPHAGEAL CANCER IN CHINA. (Eng.) Anonymous. *Lancet* 1(7922):1413-1414; 1975.

- 6506 INCIDENCE OF SPONTANEOUS NEOPLASMS IN F344 RATS THROUGHOUT THE NATURAL LIFESPAN. (Eng.) Sass, B. (Microbiological Associates, Biggs Ford Rd., Walkersville, Md. 21793); Rabstein, L. S.; Madison, R.; Nims, R. M.; Peters, R. L. *J. Natl. Cancer Inst.* 54(6):1449-1456; 1975.

- 6507 INFERRING SIGNIFICANCE FROM ANATOMIC AND CLINICAL DATA ON CANCER OF THE BREAST: A COMPUTER STATISTICAL ANALYSIS [abstract]. (Eng.) Ninfo, V. (Inst. Pathological Anatomy, Univ. Padova, 35100 Padova, Italy); Fintuzzo, D.; Pilotto, G.; Rugge, M. *IRCS Med. Sci.* 3(10):520; 1975.

- 6508 A TWO-DIMENSIONAL TLC PROCEDURE FOR ESTIMATING AFLATOXINS IN CORN [abstract]. (Eng.) Alexander, R. J. (Krause Milling Co., 4222 W. Burnham, Milwaukee, Wis. 53215); Baur, M. C., III. *Cereal Foods World* 20(9):442; 1975.

- 6509 QUANTITATIVE DETERMINATION OF THE PROLIFERATION KINETICS OF HUMAN BONE MARROW DURING INCUBATION FOR THREE DAYS. (Ger.) Boll, I.

(Stadtischen Krankenhaus Berlin-Neukölln, West Germany); Collmann, H.; Aust, C. *Blut* 31(4):201-212; 1975.

6510 NUCLEAR MAGNETIC RESONANCE STUDIES OF CANCER. VI. RELATIONSHIP AMONG SPIN-LATTICE RELAXATION TIMES, GROWTH RATE, AND WATER CONTENT OF MORRIS HEPATOMAS. (Eng.) Hollis, D. P. (Johns Hopkins Univ. Sch. Medicine, 725 N. Wolfe St., Baltimore, Md. 21205); Saryan, L. A.; Eggleston, J. C.; Morris, H. P. *J. Natl. Cancer Inst.* 54(6):1469-1472; 1975.

6511 MULTIPLE MYELOMA AND RELATED DISEASES: STUDY OF CELLULAR TURNOVER [abstract]. (Eng.) Greenberg, M. L. (Mt. Sinai Sch. Med., New York, N.Y.). *Proc. Am. Assoc. Cancer Res.* 16:142; 1975.

6512 RELATIONSHIP BETWEEN THE TIME OF DOUBLING OF PULMONARY TUMORS AND THE UPTAKE OF LABELED BLEOMYCIN. (Fre.) Cheguillaume, J. (Centre Paul-Papin, F 49036 Angers Cedex, France); Minier, J.; Tuchais, C.; Tuchais, E.; Lenk, S.; Oury, M. *Rev. Fr. Mal. Respir.* 3(Suppl. 1):221-226; 1975.

6513 THE KINETICS OF CULTURED HUMAN GLIOMA CELLS: AUTORADIOGRAPHIC STUDIES. (Eng.) Hoshino, T. (Dept. Neurological Surgery, Univ. California, San Francisco, Calif. 94143); Barker, M.; Wilson, C. B. *Acta Neuropathol. (Berl.)* 32(3):235-244; 1975.

6514 KINETICS OF HUMAN LYMPHOCYTE PROLIFERATION: PROPORTION OF CELLS RESPONSIVE TO PHA AND CORRELATION WITH E ROSETTE FORMATION. (Eng.) Nowell, P. C. (Univ. Pennsylvania, Philadelphia); Daniele, R. P.; Winger, L. A. *Fed. Proc.* 34(3):823; 1975.

See also:

- * (Rev): 6004, 6005, 6007, 6008, 6009, 6010, 6011, 6029, 6030, 6034, 6035, 6036, 6043, 6044, 6055, 6056, 6058, 6059, 6067, 6068
- * (Chem): 6121, 6146, 6149, 6176, 6187, 6191
- * (Phys): 6197, 6203
- * (Immun): 6295, 6303
- * (Path): 6436

- 6515 ISOLATION AND CHARACTERIZATION OF DIFFERENT-SIZED NUCLEOLI FROM EHRlich ASCITES TUMOR CELLS: EVIDENCE OF DIFFERENT NUCLEOLAR RIBOSOMAL CISTRONS. (Eng.) Higashi, K. (Osaka Univ. Medical Sch., Dojimahamadori, Fukushimaku, Osaka, Japan); Kohno, M.; Nishinaga, K.; Hanasaki, N.; Shikichi, K.; Takatsuka, Y.; Sakamoto, Y. *Exp. Cell. Res.* 93(2):299-308; 1975.

A procedure was developed for isolation of variously sized nucleoli in order to study the mechanism of nucleolar formation from multiple nucleolar organizers and to compare the compositions of different-sized nucleoli from Ehrlich ascites tumor cells. Relatively small nucleoli and large nucleoli from Ehrlich ascites tumor cells were separated by centrifugation at $400 \times g$ for five minutes in a layer of 0.34 M sucrose over 0.88 M sucrose. Small nucleoli remained in the 0.34 M sucrose layer, while the large nucleoli accumulated in the 0.88 M sucrose. Three fractions were separated and were provisionally named small, intermediate and large nucleoli; they contained 0.33, 0.41 and 0.84 pg DNA per nucleolus, respectively. Unfractionated nucleoli contained 0.59 pg DNA per nucleolus. The RNA content also increased with the size of the nucleolus, and no significant difference was observed in the RNA/DNA ratios in the three fractions. Large nucleoli incorporated more [^3H]uridine and [^{32}P]orthophosphate into RNA than did small nucleoli, but the base compositions of the RNAs extracted from the different-sized nucleoli were similar. No significant fragmentation occurred on sonication of large nucleoli for three minutes, so the observed difference in the DNA contents was not due to mechanical damage of the nucleoli. The DNAs of these different-sized nucleoli were analyzed on CsCl gradients. The nucleoli contained similar percentages of satellite DNA (20-22%) that were also similar to those of total, unfractionated nucleoli. Approximately 10% of the extranucleolar DNA was satellite DNA; thus, the nucleolar fractions were probably not appreciably contaminated with extranucleolar DNA. The DNA of small nucleoli contained a slightly lower percentage (0.058%) of ribosomal cistrons than large nucleoli (0.081%). This means that the higher content of DNA in the large nucleoli is not merely due to longer sized chromatin with extra regions of the vicinity of nucleolar organizers. These results suggest that the total content of ribosomal cistrons per nucleolus is roughly proportional to the DNA content of the nucleoli, at least in Ehrlich ascites tumor cells. The number of ribosomal cistrons per nucleolus for small, intermediate and large nucleoli is 40, 60 and 130, respectively.

- 6516 RETINOIC ACID BINDING PROTEIN: OCCURRENCE IN HUMAN TUMORS. (Eng.) Ong, D. E. (Vanderbilt Univ. Sch. Medicine, Nashville, Tenn. 37232); Page, D. L.; Chytil, F. *Science* 190(4209): 60-61; 1975.

Human carcinoma extracts were examined for the specific binding protein for retinoic acid by incubation with 40 nmole all-trans-[11,12- ^3H]retinoic acid in darkness at 4 C for 4 to 5 hr. Duplicate

portions containing 8 μmole unlabeled retinoic acid were used to determine specific binding. A peak radioactivity sedimenting in the 2S region on the linear 5 to 20% sucrose gradients was observed for malignant tissue from human lung (three carcinomas) and breast (one carcinoma). Corresponding normal tissues showed no specific binding protein at 2S, only the nonspecific binding protein at 4.6S. Binding was diminished by excess all-trans-retinoic acid only, but not by retinol, retinal, or oleic acid. The molecular weight of this protein is about 15,000 daltons as calculated from sedimentation data. This protein was also found in the normal human uterus. The occurrence of a cellular retinoic acid binding protein indicates that in some malignant tissues there is an altered interaction of retinoic acid within the cell as compared to normal tissue.

- 6517 SELECTIVE EFFECTS OF INHIBITORS OF PROTEIN SYNTHESIS ON METABOLISM OF NUCLEAR AND CYTOPLASMIC PROTEINS: EVIDENCE FOR COORDINATE SYNTHESIS OF NON-HISTONE CHROMOSOMAL PROTEINS. (Eng.) Vidali, G. (Rockefeller Univ. New York, N.Y. 10021); Karn, J.; Allfrey, V. G. *Proc. Natl. Acad. Sci. U.S.A.* 72(11):4450-4454; 1975.

The effects of inhibitors of protein synthesis on the metabolism of nuclear and cytoplasmic proteins of HeLa S-3 cells were studied. L-1-tosylamido-2-phenylethyl chloromethyl ketone (TPCK) (25 $\mu\text{g/ml}$) inhibition was 60%, 87%, and 25% for total cellular proteins, acid-soluble nuclear proteins (mainly histones), and non-histone nuclear proteins, respectively. Synthesis of all histone classes was suppressed by TPCK. At 0.5 μM pactamycin, [^3H]leucine uptake as a percentage of the controls, was 14.5% for nuclear nonhistone proteins, 8.8% for total cellular proteins, and 5.7% for histones. [^3H]leucine incorporation into proteins of molecular wt above 90,000 was increased by addition of TPCK to cytoplasmic but not nuclear non-histone proteins. Selective inhibition of amino acid incorporation by TPCK may be useful for the study of chromosomal and DNA-binding proteins.

- 6518 α_1 -ACID GLYCOPROTEIN AS A HEPATOCYTE-SPECIFIC MITOSIS-INHIBITING PROTEIN IN REGENERATING RAT LIVER. (Eng.) Onda, H. (Faculty Medicine, Univ. Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113, Japan); Yoshikawa, J.-I. *Gann* 66(3): 227-235; 1975.

The cellular distribution of a hepatocyte-specific mitotic inhibitor was examined in resting and regenerating liver, and in non-hepatic control tissues. The inhibitor was isolated from the plasma of normal adult male Wistar rats and found by electrophoretic and immunoelectrophoretic criteria to be pure. The molecular wt of the glycoprotein inhibitor was estimated by sedimentation experiments to be 42,000 daltons. The content of sialic acid was 9.3%. This inhibitor precipitated between albumin and α_1 -antitrypsin in immunoelectrophoresis, and thus appears to be α_1 -acid glycoprotein. Blocks of tissue

for study were fixed and then incubated for 2 hr with antibody that had been raised to the inhibitor in rabbits. After rinsing, antibody-antigen complexes were detected by further incubating the samples with goat antibody to rabbit immunoglobulin labeled with fluorescein isothiocyanate. In normal resting adult liver, positive fluorescence was located in the cytoplasm of almost all the hepatocytes, while in regenerating liver, the number of fluorescence-negative cells increased with time after partial hepatectomy. Most of the cells with brightly and diffusely fluorescent cytoplasm had round nuclei. Preparations of control tissues (brain, tongue, and cardiac muscle) did not display any fluorescence. The results suggest that the accumulation of the inhibitor within hepatocytes may suppress cell division. The accumulation may be caused by the inhibition of the secretion of endogenously-synthesized inhibitor from the cells by high extracellular concentrations of the material. Neoplastic cells may have lost the ability to respond to high levels of the inhibitor by switching-off cell division.

- 6519 TUMOR-SELECTIVE INHIBITION OF THE INCORPORATION OF ^3H -LABELED AMINO ACIDS INTO PROTEIN BY CYANATE. (Eng.) Lea, M. A. (New Jersey Medical Sch., Newark, N.J. 07103); Koch, M. R.; Morris, H. P. *Cancer Res.* 35(9): 2321-2326; 1975.

To examine the effect of cyanate on nuclear protein synthesis, ^3H -labeled amino acids (50 or 20 $\mu\text{Ci}/100\text{ g}$) were injected ip into male Buffalo rats. Groups totaling 251 rats had tumors transplanted bilaterally, sc. The tumors used and the weight range of the animals at the time they were killed were: hepatoma 5123C generation 112 (265-325 g), hepatoma 7777 generations 120 to 122 (170-250 g), hepatoma 9618A generation 9 (320-400 g), hepatoma 9618A₂ generation 114 (130-170 g), and kidney tumor MK3 generation 17 (280-340 g). Sodium cyanate at a dose level of 125 or 250 mg/kg, ip caused an inhibition of incorporation of ^3H -labeled amino acids into cytoplasmic and nuclear proteins of the rapidly growing hepatoma 7777 and the slow growing hepatoma 9618A. There was no inhibitory effect on ^3H -labeled amino acid incorporation into protein in the livers of rats bearing these tumors. Studies on the effects of sodium cyanate on incorporation of ^3H -labeled amino acids into total acid-insoluble material indicated that a greater than 85% inhibition could be achieved in hepatoma 5123C, hepatoma 9618A₂, and the MK3 kidney tumor with either little or no effect in host liver, kidneys, brain, skeletal muscle, intestinal mucosa, and regenerating liver after partial hepatectomy. The inhibition of DNA synthesis by cyanate prompted the speculation that cyanate may be an inhibitor of ribonucleotide reductase activity resembling hydroxyurea. In the rats bearing hepatoma 7777 the gross appearance of the host liver 24 hr after receiving 250 mg/kg sodium cyanate suggested the development of fatty liver and may be a reflection of effects on hepatic metabolism.

- 6520 DEPOSITION OF HISTONES ONTO REPLICATING CHROMOSOMES. (Eng.) Jackson, V. (Dept. Biochemistry, Univ. Iowa, Iowa City, Iowa 55242); Granner, D. K.; Chalkley, R. *Proc. Natl. Acad. Sci. U.S.A.* 72(11):4440-4444; 1975.

An attempt has been made to determine how the pre-existing histone molecules that are associated with DNA before replication are distributed among the progeny DNA molecules after replication. It has been suggested: (i) that these histones may be retained by the parent DNA strands in a semi-conservative fashion; (ii) that they may be acquired preferentially by one of the double-stranded daughter DNA molecules in a conservative fashion; (iii) that they may be redistributed in a completely random manner. The newly-synthesized DNA of hepatoma tissue culture cells was density-labeled with a pulse of iododeoxyuridine, and newly-synthesized histones were pulse radiolabeled with ^3H -lysine either before, concomitant with, or after the density-labeling process. The cells were then allowed to pass through several rounds of replication in media containing chases to both labels in order to produce progeny DNA molecules whose relative content of parent:daughter DNA strands could be distinguished on the basis of density. Chromatin was isolated from the cells at the end of each round of replication and applied to CsCl-density equilibrium gradients. There was no evidence of any preferential association of newly-synthesized histone material with newly-synthesized DNA in any of the labeling sequences examined. Strictly analogous data were obtained with [^3H]arginine. As histones do not turn over significantly, it is concluded that pre-existing histones are also randomly dispersed onto daughter DNA molecules during replication.

- 6521 REGULATION OF CELL CYCLE STAGE-SPECIFIC TRANSCRIPTION OF HISTONE GENES FROM CHROMATIN BY NON-HISTONE CHROMOSOMAL PROTEINS. (Eng.) Stein, G. (Dept. Biochemistry, Univ. Florida, Gainesville, Fla. 32610); Park, W.; Thrall, C.; Mans, R.; Stein, J. *Nature* 257(5529): 764-767; 1975.

In vitro transcription of histone mRNA and the regulation of transcription of information for histone synthesis was studied. The 7-12S RNAs which directed the synthesis of all five classes of histones in a cell-free protein synthesizing system from wheat germ, were isolated from polysomes of S phase HeLa S₃ cells. Poly(A)-containing RNAs were removed. The ^3H -cDNA hybridized to S phase chromatin transcripts with a $C_0t_{1/2}$ of 2.1×10^{-1} ; no hybridization above the background level of 3% was detected with G₁ transcripts. When control RNA was annealed with the cDNA no significant level of hybridization was observed. RNA isolated from S phase chromatin in the absence of carrier showed no hybrid formation with the cDNA. Endogenous histone-specific sequences associated with S phase chromatin did not contribute significantly to the hybridization observed with S phase *in vitro* transcripts. RNA transcripts from chromatin reconstituted with S phase non-histone chromosomal pro-

teins hybridized with histone cDNA. Those from chromatin reconstituted with G₁ non-histone chromosomal proteins did not. The amounts of RNA transcribed and the recoveries during isolation of these transcripts from the native and reconstituted chromatin preparations were essentially identical. Thus, RNA transcripts from chromatin of S phase but not G₁ cells contain histone-specific sequences. Transcription of histone genes is regulated during the cell cycle; non-histone proteins have a key role in this regulation.

- 6522 MEMBRANE-BOUND RIBOSOMES OF MYELOMA CELLS: I. PREPARATION OF FREE AND MEMBRANE-BOUND RIBOSOMAL FRACTIONS--ASSESSMENT OF THE METHODS AND PROPERTIES OF THE RIBOSOMES. (Eng.) Mechler, B. (Dept. Biochemistry, Univ. Cambridge, England); Vassalli, P. *J. Cell Biol.* 67(1):1-15; 1975.

A cell fractionation procedure that allows the separation of the cytoplasmic free and membrane-bound MOPC 21 (P3K) mouse plasmacytoma cell ribosomes in fractions devoid of mutual cross-contamination is described. In addition, the polyribosomal structure can be entirely preserved. This is achieved by sedimentation on a discontinuous sucrose density gradient in which the two ribosome populations migrate in opposite directions. A variety of controls (electron microscopy, labeling of membrane lipids, further repurification of the isolated fractions) provided no evidence of cross-contamination of these populations. However, when an excess of free 60S or 40S subunits, labeled with a different isotope, was added to the cytoplasmic extract before fractionation, the possibility of a small amount of trapping and/or adsorption of free ribosomal particles by the membrane fraction was detected, especially in the case of the 60S subunits; this could be entirely prevented by the use of sucrose gradients containing 0.15 M KCl. EDTA treatment of the membrane fraction detached almost all the 40S subunits, and about 70% of the 60S subunits KCl 0.5 M detached only 10% of the ribosomal particles, which consist of the native 60S subunits and the monoribosomes, i.e., the bound particles inactive in protein synthesis. Analysis in CsCl buoyant density gradients of the free and membrane-bound polyribosomes and of their derived 60S and 40S ribosomal subunits showed that the free and membrane-bound ribosomal particles have similar densities.

- 6523 INITIATION OF PROTEIN SYNTHESIS IN EHR- LICH ASCITES TUMOUR CELLS: EVIDENCE FOR PHYSIOLOGICAL VARIATION IN THE ASSOCIATION OF METHIONYL-tRNA_f WITH NATIVE 40-S RIBOSOMAL SUB- UNITS *IN VIVO*. (Eng.) Pain, V. M. (Hosp. for Tropical Diseases, 4 St. Pancras Way, London, Great Britain NW1 2PE); Henshaw, E. C. *Eur. J. Biochem.* 57(2):335-342; 1975.

To determine whether binding of methionyl-transfer RNA_f (Met-tRNA) to native 40S ribosomal subunits is subject to modulation by physiological condi-

tions, the extent of this binding in Ehrlich ascites tumor cells under nutritional conditions known to affect the rate of protein synthesis in these cells was estimated. Deprivation of either an essential amino acid, lysine, or of glucose, resulted in a substantial reduction in the proportion of native 40S subunits which had Met-tRNA_f associated with them, and refeeding of lysine partially reversed this effect within ten minutes. These effects on the concentration of Met-tRNA x 40S-subunit complexes were paralleled by changes of similar magnitude in the rate of protein synthesis and in polyribosome profiles. Native 40S subunits could be separated by equilibrium density gradient analysis on CsCl into two species, with buoyant densities approximately 1.40 and 1.49 g x cm⁻³. In cells deprived of either lysine or glucose, the radioactivity from [³⁵S]methionine was bound exclusively to the particle of buoyant density 1.40 g x cm⁻³. In well-fed cells, or in starved cells shortly after refeeding, a significant proportion of the label was associated with a region of the CsCl gradient corresponding to a particle of higher density. The results suggest that the binding of Met-tRNA_f to native 40S ribosomal subunits can be greatly affected by physiological conditions that alter the rate of protein synthesis. This is consistent with a regulatory role for this step in the sequence of reactions involved in initiation of translation.

- 6524 IDENTIFICATION OF DISCRETE ELECTRO- PHORETIC COMPONENTS AMONG THE PRODUCTS OF MITOCHONDRIAL PROTEIN SYNTHESIS IN HeLa CELLS. (Eng.) Costantino, P. (California Inst. Technology, Pasadena, Calif. 91125); Attardi, G. *J. Mol. Biol.* 96(2):291-306; 1975.

Proteins synthesized *in vivo* by HeLa cell mitochondria were characterized with respect to their electrophoretic mobility, solubility properties in organic solvents, and kinetics of labeling with [³H]isoleucine. HeLa cells (1.0 x 10⁶ to 1.5 x 10⁶ cells/ml) were treated for five minutes with 100 µg emetine/ml, a specific inhibitor of cytoplasmic protein synthesis, or with 100 µg emetine/ml plus 100 µg chloramphenicol/ml, the latter an inhibitor of mitochondrial protein synthesis; they were then exposed to L-[4,5-³H]isoleucine (30-50 Ci/mM) for various periods. The products of mitochondrial protein synthesis in whole-cell sodium dodecyl sulfate lysates were analyzed in experiments using 5 ml suspension cultures at 2.5 x 10⁶ cells/ml and L-[4,5-³H]isoleucine at 100 µCi/ml. Long-term labeling of total HeLa cell proteins was carried out by growing the cells for 48-72 hr in medium containing lysine and arginine (2 x 10⁻⁴ M each) with the addition of L-[¹⁴C]-lysine and L-[¹⁴C]arginine (318 Ci/mol each). The protease inhibitor phenylmethylsulfonylfluoride (1.0 mM) was added to the cell homogenate in some experiments. Samples of sonically disrupted 5,000 x g mitochondrial fraction or of the pellets obtained by high or low speed centrifugation of the sonicate were subjected to neutral chloroform/methanol extraction. Samples for polyacrylamide gel electrophoresis were dissolved in 2.5% sodium

dodecyl sulfate and brought to 5% mercaptoethanol. A progressive decrease in the overall rate of labeling of the mitochondrial protein products was observed in the presence of emetine, probably reflecting an indirect effect of this drug on the rate of mitochondrial protein synthesis. Ten distinct electrophoretic components in the molecular weight range 11,000-42,000 were identified with high reproducibility among the products of mitochondrial protein synthesis. The control experiments involving direct sodium dodecyl sulfate lysis of whole pulse-labeled cells or the use of the antiprotease inhibitor during cell homogenization and fractionation, excluded the possibility that the discrete electrophoretic components resulted from enzymatic degradation during extraction and fractionation, excluded the possibility that the discrete electrophoretic components resulted from enzymatic degradation during extraction. Neutral chloroform/methanol extraction resulted in a 20- to 30-fold purification with respect to the cytoplasmically synthesized proteins. The discrete electrophoretic components detected in these experiments have not yet been identified with individual polypeptide species, but both the number and size of these components agree reasonably well with the number and size of the molecular species that have been identified in yeast and *Neurospora* mitochondria as products of mitochondrial protein synthesis.

- 6525 TISSUE SPECIFIC DIFFERENCES IN THE 2'-O-METHYLATION OF EUKARYOTIC 5.8S RIBOSOMAL RNA. (Eng.) Nazar, R. N. (Baylor Coll. Medicine, Houston, Tex. 77025); Sitz, T. O.; Busch, H. *FEBS Lett.* 59(1):83-87; 1975.

In a preliminary attempt to understand the role of modified nucleotides, eukaryotic 5.8S ribosomal RNAs from various tissues of different growth rates were studied for the presence of 2'-O-methylated nucleotides and pseudouridylic acid residues. The tissues used included Novikoff ascites hepatoma cells, mouse myeloma MPC-11, HeLa cells, regenerating rat liver, and a transplanted dimethylbenzanthracene-induced mouse mammary tumor. RNA was also obtained from mouse and secondary chick embryo cells; the mammary gland of a pregnant mouse; normal rat liver; and normal mouse liver, spleen, and kidney. ³²P-labeled 5.8S ribosomal RNA was digested with pancreatic or T₁ ribonucleases and the resulting nucleotides were fractionated by two-dimensional electrophoresis. The modified fragments were identified. Pseudouridylic acid content, studied in hepatoma, myeloma, HeLa cell, normal liver, and chick embryo 5.8S ribosomal RNA, was relatively constant. The level of 2'-O-methylation for Gm-Gp fragments was high in all tissues of human, rat, mouse, or chick origin. In contrast, the 2'-O-methyl uridine content varied widely; the highest was 0.72 M in normal rat liver and the lowest was 0.17 in HeLa cells. In a series of related tissues, the lowest levels of methylation were observed in the tumor. However, there was some correlation with growth rate and it is not clear whether this change is required in malignant transformation.

- 6526 STUDIES ON NUCLEIC ACIDS IN LYMPHOCYTES OF CHRONIC LYMPHOCYTIC LEUKAEMIA. (Eng.) Billington, R. (Christie Hosp., Manchester, England); Itzhaki*, R. F. *Acta Haematol. (Basel)* 54(4):242-247; 1975.

RNA and protein synthesis were studied in chronic lymphocytic leukemia (CLL) cells that were unstimulated by mitogen. The resting CLL lymphocytes prepared from heparinized blood by the Ficoll-Trisil gradient technique were found to contain the same amount of RNA as those prepared from the blood of normal individuals. The ratio of DNA to RNA was 2.8-2.9:1 in both cases. In terms of different molecular species, as analyzed by polyacrylamide gels, there was very little to distinguish the leukemic cells. However, a relatively large amount of low molecular weight RNA was present in the CLL cells. The products of transcription of the leukemic cell nucleus were studied by the incorporation of labeled uridine and methionine. The leukemic lymphocytes showed a build-up and apparent delay in processing of ribosomal RNA precursor when compared to normal cells; however, studies of methylation revealed that the production of mature ribosomal RNA occurs at a normal rate. The production of proteins on the ribosome of CLL cells seems likely to be faulty, as evidenced by the deficiency of active ribosomes in the leukemic cells. Studies with selective inhibitors will show whether this is due to some fault in transcription of messenger RNA.

- 6527 CHANGES IN RNA METABOLISM AND ACCUMULATION OF PRESUMPTIVE MESSENGER RNA DURING TRANSITION FROM THE GROWING TO THE QUIESCENT STATE OF CULTURED MOUSE FIBROBLASTS. (Eng.) Rudland, P. S. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Weil, S.; Hunter, A. R. *J. Mol. Biol.* 96(4):745-766; 1975.

The rates of nuclear RNA synthesis, the rates of appearance of RNA in the cytoplasm, and the breakdown and net accumulation of polyadenylic acid [poly(A)] and nonpoly(A)-containing RNA were compared in quiescent BALB/c fibroblasts and in resting fibroblasts synchronously initiated to grow by serum addition to the culture medium. Changes in the rate of synthesis of nuclear poly(A)-containing RNA and the rate of accumulation and breakdown of cytoplasmic ribosomal RNA were shown to accompany the transition from the resting to the growing cellular growth state, while the rate of synthesis of nuclear poly(A)-containing RNA and the rates of accumulation and breakdown of cytoplasmic poly(A)-containing RNA (presumptive messenger RNA) were only marginally changed. The small net increase (20-30%) in the amount of presumptive messenger RNA was considerably less than the observed increase in protein synthesis (20-30%) during this transition. Extrapolysomal poly(A)-containing ribonucleoprotein particles were also isolated from quiescent cultures that were similar to those particles obtained by treatment of polyribosomes with EDTA. These experiments suggest that the early increase in protein synthetic activity when quiescent, cul-

tured cells are induced to grow is partially caused by an increased attachment of preexisting messenger RNA molecules to free ribosomes.

- 6528 INCORPORATION OF GMP INTO SPECIFIC tRNA MOLECULES BY EXTRACTS OF EHRlich ASCITES TUMOUR CELLS. (Eng.) Itoh, T. (Sch. Medicine, Keio Univ., 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan); Haruna, I.; Watanabe, I. *Nature* 257(5524): 327-329; 1975.

An enzyme was isolated from the RNA-dependent RNA polymerase fraction of Ehrlich ascites tumor cells that catalyze the incorporation of guanosine monophosphate from guanosine triphosphate into an acid-insoluble product. The enzyme requires specific tRNA's as primers. When the whole RNA was fractionated, tRNA was about four times as active as the whole RNA, while rRNA was almost inactive. Further separation of tRNA by a reversed-phase chromatography revealed that certain tRNA's were more active as primers; the primer activity of tRNA in fraction 35 was seven times that of unfractionated tRNA. The whole RNA and tRNA extracted from *Escherichia coli* were active while rRNA was almost inactive. Among the ten purified tRNA's of *E. coli* only leucine tRNA_{II}, serine tRNA_{III}, tyrosine tRNA_I, and tyrosine tRNA_{II} were active as primers. All active tRNA's possessed the S-region in their secondary structure, suggesting that the primer activity of tRNA may be related to its structural properties. The enzymatic reaction showed an absolute requirement for primer RNA. The reaction was not inhibited by creatine phosphate or creatine phosphokinase, or by inorganic phosphate; this suggests that guanidine triphosphate is the actual substrate. *E. coli* tyrosine tRNA_{II} lost all of its primer activity after oxidation by periodate or after digestion with RNase T₁. Various other nucleic acids from Ehrlich ascites tumor and *E. coli* were inactive as primer; none of these RNA's were inhibitory to the enzyme reaction. The radioactive product synthesized by the enzyme with tyrosine tRNA_{II} had a molecular size of about 4S. RNA's from mouse spleen, kidney, and liver, were inactive as primers. RNA's from tissues of mice infected with Friend virus or transplanted with Friend virus induced solid tumor, and RNA's from Friend virus-induced ascites tumor and sarcoma 180 were active. These results suggest that primer RNA's from mice are specific to tumors or tissues infected with tumor viruses.

- 6529 RNA FRAGMENTS, NECESSARY FOR THE RELEASE OF DNA REPLICATION *IN VITRO*. (Fre.) Beljanski, M. (Service de Biochimie Cellulaire, Institut Pasteur, 28, rue du Docteur-Roux, 75015 Paris, France); Beljanski, M.; Plawewski, M.; Bour-garel, P. *C. R. Acad. Sci. [D] (Paris)* 280(3): 363-366; 1975.

An attempt was made to obtain a range of RNA fragments each having, because of its configuration and composition, a selective affinity for a given type of DNA. The *Escherichia coli* M 500 Sho-R with

ribosomal RNA rich in guanine and adenosine nucleotides was used as the source. After degradation of the *E. coli* with pancreatic RNases, the RNA fragments were separated on a Sephadex column and characterized by base composition, absorption of UV light, reaction to stains, and molecular mass. The RNA fragments rapidly increased *in vitro* replication of DNA from a variety of human, animal, bacterial, and viral sources. Bacterial DNA polymerase inhibited the reactions. The priming effect of the RNA fragments was selective, even for different organs of the same animal. Possible modes of action of the RNA fragments are discussed.

- 6530 CHANGES IN LECTIN-INDUCED DEOXYRIBONUCLEIC ACID SYNTHESIS IN CULTURES OF CHICK-EMBRYO FIBROBLASTS AT VARIOUS STAGES OF DEVELOPMENT. (Eng.) Roguet, R. (Laboratoire de Biochimie, Centre de Recherches sur les Proteines, Faculte de Medecine Lariboisiere, Saint Louis [Universite Paris VII], 45 Rue des Saints Peres, 75006 Paris, France); Bourrillon, R. *Biochem. J.* 152(2):421-423; 1975.

The effects of concanavalin A and *Robinia pseudo-acacia* lectin on ³H-thymidine incorporation into acid-insoluble material of fibroblasts cultured from chick embryos at different stages of development were determined. Both lectins inhibited ³H-thymidine incorporation 40-60% in six- to ten-day embryo cells. In contrast, ³H-thymidine incorporation was stimulated 10-20% in 16-day embryo cells by both lectins. Maximal inhibition or stimulation of ³H-thymidine incorporation was obtained with 3 µg/ml solutions of the two lectins, and increasing the concentration to 100 g/ml did not significantly change these effects. In 12-day embryo cells, thymidine incorporation was not affected by lectins at any concentration. The ability of low lectin concentrations to decrease ³H-thymidine incorporation in rapidly proliferating fibroblasts indicates that lectins do not have a toxic effect. The rate of thymidine uptake at 2 C, under conditions in which DNA synthesis is inhibited, was not significantly affected by either concanavalin A or *Robinia* lectin. If the relative rate of thymidine transport at 2 C is an indication of transport at 37 C, the lectin-induced inhibition of ³H-thymidine incorporation reflects a decrease in the rate of DNA synthesis, rather than a modification of ³H-thymidine permeability. The effects of concanavalin A and *Robinia* lectin were specifically inhibited by α-methyl mannopyranoside and by anti-*(Robinia* lectin) serum, respectively. These results underline the similarity between young embryo cells and tumor cells.

- 6531 ESSENTIAL ARGINYL RESIDUES IN REVERSE TRANSCRIPTASE. (Eng.) Borders, C. L., Jr. (Harvard Medical Sch., Boston, Mass. 02115); Riordan, J. F.; Auld, D. S. *Biochem. Biophys. Res. Commun.* 66(2):490-495; 1975.

The effects of the modification of arginyl residues on the activity of reverse transcriptases were examined. The reverse transcriptase of avian

myeloblastosis virus (AMV) is rapidly inactivated (with a half life of 4 min) by incubation with 15 mM butanedione in 50 mM borate buffer at pH 8.3. By analogy to studies on other enzymes, it is presumed that the loss of activity is caused by the modification of essential arginyl residues by the butanedione. The presence of 1.3 μ M polyriboadenylic acid (poly rA) protects the enzyme to a significant extent, 69% of the control activity being retained after 10 min as compared with only 15% in its absence. It is likely that the poly rA protects the reverse transcriptase by binding to the RNA template site. Neither 0.2 mM thymidine triphosphate (TTP), an enzyme substrate, nor 2.5 μ M oligodeoxythymidylate (oligo dT), an enzyme initiator, provided any significant protection, although this concentration of oligo dT enhanced the degree of protection afforded by poly rA (to 90% of the control activity after 10 min). This additional protection may be due to shielding of additional arginyl residues at a site to which the oligo dT can only bind if the template site is already occupied. The failure of TTP to protect against inactivation, even when present at a concentration which is twenty times its K_m , seems to imply that arginyl residues do not play a role in the binding of this nucleotide substrate to the active site. However, the possibility cannot be excluded that arginyl residues are involved, but are modified by the butanedione at a much slower rate than those involved in template binding. The reverse transcriptases from feline leukemia virus and from woolly monkey virus are also inactivated by similar treatment with butanedione in borate; the decreases in activity occur with half-lives of 8 min and 16 min, respectively. The authors conclude that arginyl residues are involved in the functional binding of the RNA template to the reverse transcriptase from AMV, and are also essential to the activity of reverse transcriptases from other sources.

- 6532 THE HUMAN LEUKOCYTE TEST SYSTEM: IV. THE RNA-SYNTHESIS PATTERN IN THE FIRST G_1 -PHASE OF THE CELL CYCLE AFTER STIMULATION WITH PHA. (Eng.) Beek, B. (Institut für Genetik der Freien Universität Berlin, I Berlin 33, Arnimallee 5-7, West Germany); Obe, G. *Mutat. Res.* 29(1): 165-168; 1975.

The RNA synthesis pattern in the first G_1 -phase of the cell cycle after stimulation with phytohemagglutinin (PHA) was investigated. Four leukocyte cultures were established in 2 days and each included 10 ml medium, 0.3 ml PHA, 2.0 mg dihydrostreptomycin, 200 IU penicillin, and 0.6 ml venous blood from a healthy adult male. At each time two parallel cultures were set up. On the second day, samples were taken every two hr; this procedure provided two parallel samples for each hour from 1 to 25 hr after culture initiation. RNA synthesis was determined by adding 1 μ Ci [3 H]uridine to each sample 15 min before stopping culture growth. Autoradiographs were made and the percentages of labeled interphase nuclei were determined. The results from the two parallel series were

similar. A low level of RNA-synthesizing nuclei was found up to 12 hr after culture initiation. RNA synthesis increased in both series after 13 hr. First maxima were reached at 14 and 15 hr, for the first and second series, respectively. Second maxima were reached at 19 hr and 20 hr, respectively. Troughs occurred at 16 hr and at 23 hr (nearly identical for both series). In both experimental series, the results showed a biphasic distribution of RNA-synthesis maxima. The authors suggest that biphasic distribution of RNA-synthesis maxima may be correlated with the biphasic DNA-synthesis pattern and the two mitotic waves occurring in this leukocyte culture.

- 6533 NUCLEAR DNA POLYMERASES AND THE HeLa CELL CYCLE. (Eng.) Chiu, R. W. (Worcester Foundation for Experimental Biology, Inc., Shrewsbury, Mass. 01545); Baril, E. F. *J. Biol. Chem.* 250(19):7951-7957; 1975.

The variations in the activity of two DNA-dependent DNA polymerases in purified nuclei of HeLa S_3 cells during the cell cycle of a synchronized culture were investigated. Cells were synchronized by a double thymidine block, harvested at various phases of the cycle, and the two DNA polymerases were purified partially by DEAE-cellulose and phosphocellulose chromatography. The activity of DNA polymerase I (low molecular weight, *N*-ethyl-maleimide-insensitive) remained essentially constant throughout the cycle. The activity of DNA polymerase II (high molecular weight, *N*-ethylmaleimide-sensitive), however, increased during G_1 to mid-S and declined, 7- to 10-fold between late-S and G_2 . Addition of cycloheximide (60 μ g/ml) to cultures 12 hr after the release from thymidine block abolished the rise in the activity of DNA polymerase II. Cycloheximide also reduced the activity of DNA polymerase I by 60%. Addition of hydroxyurea (1 mM) one hour after release had no effect on the activity of either enzyme. It is concluded that in HeLa cells, DNA polymerases I and II are distinct enzymes, that DNA polymerase II probably functions in DNA replication and is probably induced in response to stimuli for DNA biosynthesis.

- 6534 NUCLEAR DEOXYRIBONUCLEIC ACID POLYMERASES OF LIVER. (Eng.) Lynch, W. E. (Univ. Pittsburgh Sch. Medicine, Pittsburgh, Pa. 15261); Surrey, S.; Lieberman, I. *J. Biol. Chem.* 250(20): 8179-8183; 1975.

Evidence for the presence of two DNA polymerases in regenerating liver nuclei after partial hepatectomy is presented. The liver nuclei post-mitochondrial fractions of normal female Fischer 344 rats and rats which had been subjected 22 hr earlier to 70% hepatectomy were separated and subjected to sucrose gradient analysis to determine the distribution of DNA polymerase activity in the two fractions. The effects of the concentration and pH of Tris buffer in the homogenizing medium, the concentration of KCl in the medium, and the concentration of liver in the medium were determined as were the

distribution of enzyme activity between the two fractions and the effects of serum albumin and spermidine on the activities of the regenerating liver DNA polymerases. With nuclear and post-mitochondrial fractions prepared in low ionic strength solutions, essentially all of the DNA polymerase activity of the homogenate was recovered in the nuclei. The DNA polymerase activities of the post-mitochondrial fraction rose as the concentrations of Tris buffer and KCl in the homogenizing solution increased. Even with low ionic strength solutions, some leaching of the nuclear enzymes occurred when the concentration of liver in the homogenizing solution was greater than 10%. As indicated by sucrose gradient analysis, the normal adult rat liver nuclei contained primarily or entirely as single species of DNA polymerase (3.2S), while the regenerating nuclei contained an additional species (7.1S). The total activity in the regenerating nuclei was about twice the normal value, the increase being attributable to the 7.1S activity. Apparently identical 7.1S DNA polymerases were partially purified from regenerating liver nuclei and cytosol fractions. Albumin and spermidine markedly stimulated the activities of both the 3.2 and 7.1S DNA polymerases. In the presence of spermidine, but not in its absence, the activity of the 7.1S species was strictly proportional to the amount of enzyme. The failure of other investigators to observe the presence of two DNA polymerases in regenerating liver nuclei is probably attributable to their use of buffer and inorganic salts in the preparative solutions and their failure to add albumin and a basic molecule to the assay mixture.

- 6535 INTRACELLULAR DISTRIBUTION OF VARIOUS ENZYMES CONCERNED WITH DNA SYNTHESIS FROM NORMAL AND REGENERATING RAT LIVER, AND YOSHIDA SARCOMA. (Eng.) Shiosaka, T. (Sch. Med., Tokushima Univ., Japan); Arima, T.; Toide, H.; Okuda, H.; Fujii, S. *J. Biochem. (Tokyo)* 77(1):249-256; 1975.

The subcellular distribution of enzymes concerned with DNA synthesis were examined in order to determine whether these exist as a complex of several DNA synthetic enzymes in a functional unit associated with a membrane component. During the fractionation of the enzymes from the postmicrosomal supernatant fraction of various tissues, DNA polymerase, thymidine kinase, deoxythymidine monophosphokinase (dTMP kinase), deoxycytidine kinase, and deoxycytidine monophosphokinase (dCMP kinase) were found in the pellet fraction of postmicrosomal supernatant. The uridine kinase and aspartate transcarbamylase activities of postmicrosomal supernatant from various tissues were also present in this pellet fraction. The activities of DNA polymerase, thymidine kinase, uridine kinase, and aspartate transcarbamylase from normal and regenerating rat liver, and from Yoshida sarcoma were higher in the pellet fraction than in the supernatant. The activities of dTMP kinase, dCMP kinase, and orotidine-5'-phosphate decarboxylase were lower in the pellet fraction than in the supernatant.

The pellet fractions of regenerating rat liver and Yoshida sarcoma showed a remarkable incorporation of various precursors (thymidine, dTMP, deoxycytidine, and dCMP) into DNA in the presence of a suitable DNA template, ATP, and all four deoxynucleoside 5'-triphosphates for DNA synthesis. Normal adult rat liver catalyzed a much smaller incorporation of all these precursors, except for dCMP. The study confirms that the postmicrosomal supernatant fraction from proliferating tissues contains various enzymes concerned with DNA synthesis in addition to DNA polymerase and ribonucleotide reductase.

- 6536 DIFFERENTIAL EFFECTS OF DIBUTYRYL CYCLIC AMP ON THE GROWTH AND MORPHOLOGY OF AN ESTABLISHED HUMAN LYMPHOCYTE LINE. (Eng.) Smith, S. W. (Methodist Hosp., 506 Sixth St., Brooklyn, N.Y. 11215); Werthamer, S.; Artman*, M. *In Vitro* 10(3/4):225-229; 1974.

The effects of dibutyryl cyclic AMP on the growth and morphology of RPMI 1788 lymphocytes were studied. In the absence of dibutyryl cyclic AMP, lymphocytes grown in a semisuspension culture proliferated as separate cells and in clumps. Addition of 10^{-3} M dibutyryl cyclic AMP to the culture resulted in the attachment of the cells to the substratum and in a subsequent conversion of a portion of the adherent cells to a fibroblast-like morphology. Growth of the adherent cells proceeded at nearly the same rate as that of control cells. When cells cultured in the presence of dibutyryl cyclic AMP were periodically disturbed, they remained in suspension and under this condition a distinct inhibition of growth by dibutyryl cyclic AMP was observed. Cortisol at 10^{-3} M had no effect on the proliferation of RPMI 1788 cells; however, 10^{-3} M cortisol in combination with dibutyryl cyclic AMP prevented cell attachment, caused detachment of already adherent cells, and thus brought about the dibutyryl cyclic AMP-mediated inhibition of growth in suspension. At a higher concentration (10^{-4} M) cortisol alone reduced the growth rate of RPMI cells. Under the combined effects of 10^{-4} M cortisol and 10^{-3} M dibutyryl cyclic AMP the proliferation and viability of cells in suspension were significantly lower than in the presence of either agent alone. Clarification of cyclic AMP-hormonal interactions may further the understanding of the molecular basis of the regulation of cell growth.

- 6537 DNA BINDING BY CYCLIC ADENOSINE 3',5'-MONOPHOSPHATE DEPENDENT PROTEIN KINASE FROM CALF THYMUS NUCLEI. (Eng.) Johnson, E. M. (Rockefeller Univ., New York, N.Y. 10021); Hadden, J. W.; Inoue, A.; Allfrey, V. G. *Biochemistry* 14(17):3873-3884; 1975.

Cyclic AMP (cAMP)-dependent protein kinase and proteins specifically binding cAMP were extracted from calf thymus nuclei and analyzed for their abilities to bind to DNA. Approximately 70% of

the cAMP-binding activity in the nucleus could be ascribed to a nuclear acidic protein with physical and biochemical characteristics of the regulatory (R) subunit of cAMP-dependent protein kinase. Several peaks of protein kinase activity and of cAMP-binding activity were resolved by affinity chromatography of nuclear acidic proteins on calf thymus DNA covalently linked to aminoethyl Sepharose 4B. When an extensively purified protein kinase was subjected to chromatography on the DNA column in the presence of 10^{-7} M cAMP, the R subunit of the kinase was eluted from the column at 0.05 M NaCl, while the catalytic (C) subunit of the enzyme was eluted at 0.1-0.2 M NaCl. When chromatographed in the presence of histones, the R subunit was retained on the column and was eluted at 0.6-0.9 M NaCl. In the presence of cAMP, association of the subunit with DNA was enhanced, as determined by sucrose density gradient centrifugation of DNA-protein complexes. cAMP increased the capacity of the calf thymus cAMP-dependent protein kinase preparation to bind labeled calf thymus DNA, as determined by a technique employing filter retention of DNA-protein complexes. This protein kinase preparation bound calf thymus DNA in preference to salmon DNA, *Escherichia coli* DNA, or yeast RNA. Binding of protein kinases to DNA may be part of a mechanism for localizing cyclic nucleotide stimulated protein phosphorylation at specific sites in the chromatin.

- 6538 CYCLIC AMP-DEPENDENT PROTEIN KINASE: PIVOTAL ROLE IN REGULATION OF ENZYME INDUCTION AND GROWTH. (Eng.) Insel, P. A. California, Sch. Medicine, San Francisco, Calif. 94143; Bourne, H. R.; Coffino, P.; Tomkins, G. M. *Science* 190(4217):896-898; 1975.

Dibutyl cyclic AMP produced phosphodiesterase induction, growth arrest, and cytolysis in cultured wild-type S49 lymphoma cells. These cells and three classes of clones resistant to cyclic AMP were compared with respect to (i) activity in cell lysates of cyclic AMP-dependent protein kinase, assessed by binding of ^3H -labeled cyclic AMP or by cyclic AMP-stimulated phosphorylation of histone, and to (ii) the biological effects of dibutyl cyclic AMP on phosphodiesterase induction, growth inhibition in G_1 , and cellular proliferation. Cyclic AMP concentrations required by one variant for half-maximal stimulation of histone phosphorylation or cyclic AMP binding were approximately ten times higher than in wild-type cells. The variant cells also required about ten times more dibutyl cyclic AMP for equivalent growth inhibition and enzyme induction. In the second variant, maximal cyclic AMP binding and cyclic AMP stimulation of kinase activity were about half the value measured in wild-type cells. Similarly, maximally effective dibutyl cyclic AMP concentrations produced only about half the phosphodiesterase induction and growth inhibition observed in wild-type cells. The third variant was completely resistant to dibutyl cyclic AMP and lacked both cyclic AMP-stimulated protein kinase activity and cyclic AMP binding. These dose-response relationships demon-

strate that protein kinase mediates cyclic AMP regulation of growth and enzyme induction in S49 cells.

- 6539 PREFERENTIAL LOCALIZATION OF CADMIUM ON ITERATIVE DNA SEQUENCES ISOLATED FROM TOBACCO CROWN-GALL TISSUE CULTURES. (Fre.) Sissoeff, I. (Universite Paris-XI, Centre d'Orsay, Laboratoire de Biologie Moleculaire Vegetale, associe au CNRS n° 40, Batiment 430, 91405 Orsay, France); Grisvard, J.; Guille, E. *C. R. Acad. Sci. [D] (Paris)* 280(20): 2389-2392; 1975.

The DNA extracted from tissue cultures of tobacco crown-gall was purified and centrifuged in a gradient of cesium sulfate with silver ions ($\text{Cs}_2\text{SO}_4\text{-Ag}^+$) and cadmium was sampled from the various fractions of the gradient. The cadmium was specifically localized in the lower density fractions of the gradient where iterative DNA is found. Possible origins of the cadmium are presented: 1) tied to the DNA *in vivo*, 2) originating from other cellular components with which the DNA molecules come into contact during extraction, or 3) a result of the extraction and purification methods. The presence of large quantities of cadmium on certain iterative DNA sequences suggests that DNA-cadmium ties do exist under physiological conditions. The preferential localization of cadmium was also verified with the isolated DNA of other plant tissues.

- 6540 INDUCTION OF ORNITHINE DECARBOXYLASE, TYROSINE AMINOTRANSFERASE, AND THYMIDINE KINASE BY GLUCOCORTICOID IN ISOLATED, PERFUSED LIVER AFTER TUMOR INOCULATION. (Eng.) Sakata, R. (Chiba Univ. Sch. Medicine, Inohana 1-8-1, Chiba 280, Japan). *Gann* 66(3):245-252; 1975.

A method was developed for determining the extent of *in vitro* enzyme induction in both the normal and malignant regions of perfused livers. In order to induce the growth of solid tumors, 10^7 ascites tumor cells of Yoshida sarcoma origin were transplanted by syringe into the margin of the median or left lateral lobes of the livers of normal male Donryu rats. After 1 wk, the livers were excised and perfused with an oxygenated medium containing calf serum, perfluorotributylamine, pluronic acid, glucose, and antibiotics. For induction studies, sodium hydrocortisone succinate (initially 2 mg/100 g plus further 1 mg/hr subsequently) was administered to the livers through the perfusion inflow cannulas. After 6 hr of perfusion, the normal tissues and tumor tissues were separately homogenized in Tris buffer, centrifuged, and the supernatants assayed for particular enzymic activities. The supernatant activity of tyrosine aminotransferase declined slightly in both normal and neoplastic tissues from livers perfused without hydrocortisone. A 3-fold stimulation in activity was observed for normal tissues in livers perfused with the glucocorticoid for 6 hr; a smaller increase (1.5-fold) was seen in the neoplastic regions. The ornithine decarboxylase activity of normal tissue increased about 1,300% over the course of a 6 hr perfusion with the glucocorticoid. In contrast, Yoshida sarcoma

tissues had only low activities of this enzyme: these activities were not increased by hydrocortisone. The activity of thymidine kinase was high in Yoshida sarcoma tissue immediately after removal of the liver from the body, but fell after 30 min of perfusion to the level of normal liver tissue and to almost zero after 6 hr. Addition of hydrocortisone during the perfusion caused a slight induction of the enzyme in the neoplastic region: this increase was not evident in normal tissue. It is apparent that the induction by hydrocortisone of the enzymes studied was quite different in the neoplastic and normal regions of the tumor-bearing perfused livers.

- 6541 ELECTRON MICROSCOPIC DEMONSTRATION OF DNA STRANDS ASSOCIATED WITH FIBRILLARY RNA ZONES OF THE NUCLEOLI IN INTERPHASIC NUCLEI OF L929 CELLS. (Fre.) Pouchelet, M. (INSERM U 104, CNRS et Association Claude-Bernard, Hopital saint-Antoine, 75571 Paris, Cedex 12, France); Gansmuller, A.; Anteunis, A.; Robineaux, R. *C. R. Acad. Sci. [D] (Paris)* 280(21):2461-2463; 1975.

Electronic opacification which uses oxidized diaminobenzidine (DAB) at pH 3 accompanied by ribonuclease enzymatic digestion made it possible to differentiate between cellular structures containing RNA and those containing DNA. A group of DNA strands associated with groups of intranucleolar DNA and with the fibrillary RNA zones of the nucleoli were detected in the fibroblast cells L929 during interphase. The detected strands of DNA are most probably actively involved in the transcription of the pre-ribosomal 45S RNA's. The dispersion of the DNA strands and their location, point to an active role of the DNA in the transcription of the nucleolar fibrillary RNA's; these represent the preribosomal RNA's. The localized ribosomal genes would be produced in fibrillary form by the intranucleolar DNA strands and the quantity would be representative of transcriptional activity. However, the reaction between the intranucleolar DNA and the preribosomal RNA synthesis activity will only be ascertained when it is determined that each intranucleolar DAB positive group of strands is in contact with one or more fibrillary zones of RNA.

- 6542 A WHITE BLOOD CELL RNase ASSAY FOR THE POSSIBLE MONITORING OF MALIGNANCY. (Eng.) Drake, W. P. (Natl. Cancer Inst., 3100 Wyman Park Drive, Baltimore, Md. 21211); Pokorney, D. R.; Ruckdeschel, J. C.; Levy, C. C.; Mardiney, M. R., Jr.* *J. Natl. Cancer Inst.* 54(6):1475-1478; 1975.

The RNase activity observed in the sera of leukemic (L2C) guinea pigs was compared to that observed in the WBC lysates of the same animals. WBC were lysed by incubation at 37 C for ten minutes with 0.2% Triton X-100. The supernatant remaining after a 15-min centrifugation at 5,000 x g was used in assays of WBC-associated RNase activity directed against polyadenylic acid, polyuridylic acid, polycytidylic acid, and polyguanylic acid.

The WBC-associated RNase activity directed against polyuridylic acid decreased with the progression of neoplastic disease, although serum RNase activity remained unchanged. With certain forms of cancer, therefore, variations in cell RNase may be more sensitive markers than changes in serum RNase for the evaluation of the progression or regression of disease.

- 6543 DIFFERENT MECHANISMS FOR THE INDUCTION OF ACETYLCHOLINESTERASE IN NEUROBLASTOMA CELLS. (Eng.) Simantov, R. (Weizmann Inst. Sci., Rehovot, Israel); Sachs, L. *Dev. Biol.* 45(2):382-385; 1975.

The postulate that dibutyryl adenosine 3':5'-cyclic monophosphate (dibutyryl-cAMP) and 5-bromodeoxyuridine (BrdU) induce acetylcholinesterase activity by different mechanisms was investigated. Mouse neuroblastoma C-1300 tumor cells were cultured in Eagle's medium, then subcultured to select clones resistant to dibutyryl-cAMP, as well as temperature-resistant cells capable of multiplying at 40 C. Acetylcholinesterase activity was assayed in dibutyryl-cAMP-resistant and nonresistant cells treated with dibutyryl-cAMP, BrdU, or cytosine arabinoside (Ara-C). Cells were preincubated for 30 min in the presence of 0.5 µg/ml actinomycin D. Incubation with 2 mM dibutyryl-cAMP induced acetylcholinesterase activity after 18 hr in nonresistant cells. It did not induce activity in resistant cells. BrdU (1 µM) or Ara-C (1 µM) produced acetylcholinesterase activity in both nonresistant and resistant cells in the absence of actinomycin D after 18 hr, but failed to produce activity in the presence of actinomycin D. Actinomycin D, BrdU and dibutyryl-cAMP inhibited DNA synthesis by 94%, 99%, and 33%, respectively. In temperature resistant cells, selected for multiplication at 40 C the induction of dibutyryl-cAMP and BrdU at 37 C was 2- to 4-fold lower than with nonresistant cells; however, the induction by dibutyryl-cAMP was 2- to 4-fold higher at 40 C than at 37 C while induction by BrdU was 2- to 3-fold lower at 40 C. The authors conclude that BrdU and dibutyryl-cAMP induce acetylcholinesterase activity in neuroblastoma cells by different mechanisms.

- 6544 CONTINUOUS PRODUCTION OF PEROXIDASE, ESTERASE, ALKALINE PHOSPHATASE AND LYSOZYME BY CLONES OF PROMYELOCYTES. (Eng.) Greenberger, J. S. (Viral Carcinogenesis Branch, Natl. Cancer Inst., Bethesda, Md. 20014); Aaronson, S. A.; Rosenthal, D. S.; Moloney, W. C. *Nature* 257(5522):143-144; 1975.

Clones were established from Jones chloroma rat leukemia and Wistar/Furth (W/Fu) acute myelogenous leukemia (AML) maintained *in vitro* for about two months, and then tested for enzyme production and for morphological appearance. Jones chloroleukemia clones (23) produced peroxidase, esterase, alkaline phosphatase, and lysozyme. W/Fu AML cells (15 clones) were indistinguishable in myeloblast morphology and in production of a single enzyme, lysozyme. The proportion of positive cells was similar in all clones tested. The *in vitro* growth parameters (doubling time, saturation density, and colony-

forming efficiency) were indistinguishable from those of the parent lines. Several Jones chloroleukemia clones were uniformly positive for C-type RNA virus after ten days in culture; however, there was no detectable change in promyelocyte morphology or in the strength of production of the four myeloid enzymes, despite continuous production of this C-type virus for more than 300 days *in vitro*. W/Fu AML cells remained virus-negative for several months in spite of growth characteristics similar to Jones chloroleukemia cells. After 150 days *in vitro*, some W/Fu AML clones produced low levels of an indistinguishable rat C-type virus, but with no change in morphology or in myeloid enzyme production. These results provide the first demonstration of the production of multiple lysosomal enzymes by clonal lines of myeloid cells and imply that all myeloid stem cells can produce multiple enzymes. The fact that only one myeloid enzyme was produced by W/Fu AML cells possessing a primitive myeloblast morphology, while several enzymes were synthesized by the more differentiated promyelocytic line, supports the finding in bone marrow preparations of low or absent levels of myeloid enzymes in morphologically undifferentiated cells.

- 6545 KINETIC DETERMINATION OF THERMOSTABLE ISOENZYMES OF ALKALINE PHOSPHATASE IN PREGNANCY AND CANCER CASES. (Bul.) Danev, S. (Dept. Clin. Lab., Med. Acad., Bulgaria); Lazarova, A. *Sovrem. Med.* 26(1):30-36; 1975.

A kinetic method for the determination of the thermostable alkaline phosphatase (AP) is proposed and the normal values for this AP during pregnancy are determined. The case material consisted of 159 healthy women between the fourth and tenth months of pregnancy, 20 women with pathological pregnancies, and 50 cancer patients. Two patients with ovarian carcinoma had a residual AP activity of 10% and 14%, respectively, after 60 min of thermal inactivation. In a patient with carcinoma of the sigmoid colon, the AP thermostability was 16%. In all the other cancer patients studied, including 26 with lung cancer and 10 with breast cancer, the thermostable AP level ranged from 0 to 5% of the general AP activity, which is within normal limits. The authors suggest that this method may also be useful for the screening of cancer patients with the Regan isoenzyme of AP.

- 6546 KINASE AND DEAMINASE ACTIVITY IN A VARIETY OF SUBCUTANEOUS MOUSE TUMORS. (Eng.) Furner, R. L. (Biochemical Pharmacology Div., Kettering-Meyer Lab., Southern Res. Inst., Birmingham, Ala. 35205); Mellett, L. B. *Cancer Res.* 35(7):1799-1803; 1975.

Extracts of solid mouse tumors were examined for deoxycytidine kinase and deaminase activities in order to determine if the inhibitory action of arabinosyl cytosine is influenced by these activities. Mice (C57, AKR, C3H, DBA, and C57BL x DBA2 F₁) were implanted sc with adenocarcinoma 755, Ridgway osteogenic sarcoma, B16 melanoma, C3H mammary carcinoma, glioma 26, CaD₂ carcinoma, Lewis lung, and Sarcoma 180 tumors. The supernatants from tissue homogenates were analyzed for kinase activity and deaminase activity

by DEAE cellulose at pH 7.4, and by instant thin layer chromatography. Tetrahydrouridine (0.341 mM) was used in some experiments. 1-β-D-Arabinofuranosylcytosine nucleotide was formed at a rate of 45 nm/hr by Glioma 26/57 and only 14 nm/hr by Ridgway osteogenic sarcoma. Some tumors, such as Lewis lung and sarcoma 180 had tremendously high levels of deaminase activity, compared with modest levels of kinase activity. Deaminase activity was highest in Lewis lung (114 of 1-β-D-arabinofuranosyluridine formed per hour) and in CaD₂ (104 nm of 1-β-D-arabinofuranosyluridine formed per hour). Deaminase activity in tumor extracts was sensitive to freezing, while deaminase activity in monkey serum not. Kinase activity varied by as much as 50% in different cell lines of the same tumor. In the presence of tetrahydrouridine, kinase activity was significantly increased in most of the tumors studied, while deaminase was reduced to near zero. Adenocarcinoma 755, sarcoma 180, or Lewis lung would all be acceptable as an *in vitro* tumor model for assessing the influence of tetrahydrouridine on the therapeutic effectiveness of arabinosyl cytosine.

- 6547 POLY (ADENOSINE DIPHOSPHORIBOSE) SYNTHASE ACTIVITY OF ISOLATED NUCLEI OF NORMAL AND LEUKEMIC LEUKOCYTES. (Eng.) Burzio, L. (Biomedical Div., The Population Council, The Rockefeller Univ., New York, N.Y. 10021); Reich, L.; Koide, S. S. *Proc. Soc. Exp. Biol. Med.* 149(4):933-938; 1975.

To determine the capacity of isolated nuclei from normal and leukemic WBC to carry out DNA synthesis, poly(adenosine diphosphoribose) (ADPR) synthase activities of the nuclei were assayed by incubation with radioactive NAD⁺ for 20 min or for 60 min (distribution determination). The materials used for the assay and estimation of the chain length of poly(ADPR) included [methyl-³H]thymidine triphosphate (18.3 Ci/mM), venom phosphodiesterase from *Crotalus adamanteus*, pancreatic DNase, spleen phosphodiesterase, [¹⁴C]PR-AMP, and WBC. For a nuclei preparation of 150-200 μg of protein, 2 mM [adenosine ³H]NAD⁺ (5 μCi/mM), or [¹⁴C adenosine] NAD⁺ (1 μCi/mM) was used. The counting efficiency for tritium was 40% and for [¹⁴C] was 70%. The synthase activity of leukemic WBC nuclei was significantly higher than that of normal WBC nuclei. The average length of polymers formed by isolated leukemic nuclei ranged from 3.1-5.3 ADPR residues per chain, while those produced by normal WBC nuclei were 1.7 and 2.6 residues per chain. Isolated leukemic and normal WBC nuclei were incubated with and without NAD⁺ and the ability to carry out DNA synthesis was measured. The endogenous DNA synthesis of NAD-treated and untreated nuclei was the same. This finding parallels the result obtained with Novikoff hepatoma cell nuclei and differs from the observation with rat liver or testis nuclei. The results suggest: (1) that poly(ADPR) was degraded by the glycohydrolase and phosphodiesterase activities which might be high in leukemic WBC nuclei; (2) that poly(ADPR) might be linked to proteins by different types of bonds with varying degrees of lability to alkali treatment or that the released polymers were large enough to be precipitated by trichloroacetic acid

and (3) that long chain polymers were dissociated from nonhistone proteins by alkali treatment.

- 6548 CARCINOFOETAL ALTERATIONS IN GLUCOSAMINE-6-PHOSPHATE SYNTHETASE. (Eng.) Tsuiki, S. (Res. Inst. for Tuberculosis, Leprosy, and Cancer, Tohoku Univ., Sendai, Japan); Miyagi, T. *Ann. N.Y. Acad. Sci.* 259:298-306; 1975.

The levels of glucosamine-6-phosphate synthetase were examined in various rat tissues, including those undergoing differentiation or regeneration. Enzyme levels were high in rat liver, submaxillary gland, and cartilage, and also in the testis, spleen and thymus, suggesting that at least a fraction of the synthetase activity has a positive correlation with cell proliferation. This hypothesis was verified when studies of regenerating rat liver showed that partial hepatectomy induced a marked rise in hepatic synthetase activity concomitantly with an increase in DNA synthesis. Rat ascites hepatomas were tested for glucosamine-6-phosphate synthetase levels and they were markedly high in all cases as compared with liver. A rat hepatoma that had been grown either ip or sc was also rich in this enzyme as was a strain of lung cancer that had been maintained by serial sc transplantation into rats; this indicates that increased glucosamine-6-phosphate synthetase activity is not a phenomenon restricted to hepatomas, but rather is characteristic of neoplasia. Assay of the enzyme from normal liver and Yoshida sarcoma indicated that although many of the kinetic properties are the same, the two enzymes differ in the sensitivity to feedback inhibition and in the salt concentration at which the enzyme is eluted from a DEAE-Sephadex column. Immunological data showed that the tumor enzyme is the second form, probably synthesized by genetic information different from that for the liver enzyme. Isoelectric focusing indicated that the hepatoma enzyme was not isozymically homogenous; there was one major peak and two additional peaks. The major tumor form was not present in fetal liver, but was found in embryos at earlier stages of development and in brain. A possible explanation for this phenomenon is that in liver with embryonic development, the original "embryonic" form of the enzyme is first replaced by a form that is predominant in late fetal liver, which is in turn replaced by the adult liver form. It is concluded that glucosamine-6-phosphate synthetase is among those enzymes whose major neoplastic alterations are carcinofetal.

- 6549 ANCHORAGE DEPENDENT CHANGES IN TRANSPORT OF GLUCOSE, ADENOSINE, URIDINE AND LEUCINE IN 3T3 CELLS. (Eng.) Otsuka, H. (Dept. Biological Sciences, Purdue Univ., West Lafayette, Indiana 47907); Moskowitz, M. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):379-387; 1975.

The pattern of uptake of glucose, adenosine, uridine, and leucine in suspension and in monolayer cultures of 3T3 cells was studied. Confluent monolayer 3T3 cells were trypsinized and suspended in modified Eagle's medium containing 10% calf serum and 1.2% Methocel at 10^5 cells/ml. The suspension was incubated for 24 hr after which the cells were transferred to suspension or monolayer culture. At different times in monolayer or suspension culture, the cells were incubated with 1 ml Earle's buffered salt solution containing 1 μ Ci [3 H]-uridine, [3 H]-adenosine or [3 H]-leucine for ten minutes. The uptake of these compounds increased linearly at least up to 20 min. For assaying uptake of [3 H]-deoxyglucose, glucose-free medium was used. At the end of the incubation, the radioactivity in the cells was counted in a liquid scintillation counter. The uptake of leucine in growth medium was determined by adding [3 H]-leucine to either monolayer or suspension cultures of 3T3 cells in modified Eagle's medium containing 10% calf serum at 12.5 μ Ci/ml and incubated. At 30 sec the cultures were immersed in an ice bath. After washing, the cells were suspended in 1 ml of cold 5% trichloroacetic acid and centrifuged. The radioactivity in trichloroacetic acid soluble and insoluble fractions was counted in a liquid scintillation counter. The rate of protein synthesis was determined in a similar manner, except that the radioactivity in the trichloroacetic acid-insoluble fraction was determined at 5-, 10- and 15-min intervals. The pattern of uptake of deoxyglucose was similar in suspension and monolayer cultures; changing the medium or adding serum stimulated uptake under both culture conditions. The uptake of uridine and adenosine was greater in suspension culture than in monolayer culture. There was a low uptake of leucine in suspension cultures relative to the uptake in sparse monolayer cultures. Cells do not multiply in suspension culture but do in monolayer cultures. It is concluded that there is a correlation between uptake of leucine and conditions which stimulate cell multiplication, but no correlation of the uptake of deoxyglucose, uridine and adenosine with these conditions. It is also concluded that serum factors play important roles in stimulating the uptake of glucose, uridine, and leucine. The variation in the stimulation of the uptake of these compounds under different culture conditions suggests that either a single serum component affects the respective transport systems differently or that different serum factors are involved in the stimulation of each transport system.

6550 RELATIONSHIP BETWEEN THE FETAL HEMOGLOBIN LEVELS AND CERTAIN TUMOR PROCESSES IN THE LIVER. (Fre.) Bladier, D. (Hopital Franco-Musulman, CHU de Bobigny, 125, route de Stalingrad, 93000 Bobigny, France); Pre, J.; Fabia, F.; Cornillot, P. *C. R. Acad. Sci. [D] (Paris)* 280(9):2583-2585; 1975.

Blood levels of fetal hemoglobin (HbF) were studied in ten patients with cirrhosis and four patients with hepatoma (adenocarcinoma of the liver). HbF blood levels were determined by an alkaline denaturation resistance method (RDA) or by quantitation of isoleucine (ILE), characteristic of the fetal hemoglobin. In the four patients with hepatoma, HbF, measured as percentage of total hemoglobin, ranged from 25-39% using the RDA method of determination and from 31.6 to 47% for the ILE method. Levels for the cirrhotic patients were considerably lower (1 to 5%) but still higher than normal levels (0.5 to 1.5%). Elevated HbF levels could not be attributed to the stimulation of each transport system.

buted to any hematological disorders in the patients with malignancy. The results confirm the supposition that fetal proteins other than α -fetoprotein are synthesized in the course of the neoplastic process in the liver.

6551 "TRANSCRIPTIONAL DOMINANCE" OF A NUCLEOLAR ORGANIZER IN CULTURED CELLS. (Eng.)

Okano, H. (Cancer Res. Inst., Kyushu Univ., Kukuoka 812, Japan); Yamana, K. *Proc. Jpn. Acad.* 51(3): 208-212; 1975.

The mechanisms of nucleolar gene cluster activity were investigated. Secondary cultures of mouse (ICR/Ha Swiss) embryo fibroblasts were infected with murine leukemic virus and labeled with $5\text{-}^3\text{H}$ -uridine. Electron microscopic autoradiography showed that more than two thirds of the cells were in the three-nucleolate state; the remainder were either in the two- or four-nucleolate. Three cell types were designated: (+ +), (+ -), and (- -); + and - being a labeled nucleolus and an unlabeled one, respectively. After 30 min of labeling, almost all incorporated radioactivity remained in the nucleus and the nucleolus. More than 70% of the cells were type (+ -); the two other types were about even in number. After 4 hr of labeling there were fewer (+ -) and (- -) type cells and type (+ +) cells had increased four times and outnumbered the type (+ -) cells, demonstrating that nucleolar genes were functioning in ribosomal RNA synthesis during the experimental period. The authors derive three implications from these observations. First, there are two phases of a nucleolar gene cluster in interphase, active (transcriptionally dominant) and inactive (transcriptionally recessive). Secondly, the genes associated with an unlabeled nucleolus are probably active before the onset of labeling and then activated throughout the labeling period. Finally, the increase in the type (+ +) cells after the longer labeling period may be partly due to the activation of previously inactive nucleolar genes. The authors propose that the alternating activation and inactivation of the nucleolar organizer may help explain the observation that each of the two "paired" nucleoli in the wild toad is smaller than the single nucleolus found in cells from a heterozygous mutant lacking one of the two nucleolar organizers.

6552 INDUCED THERMAL RESISTANCE IN HeLa CELLS.

(Eng.) Gerner, E. W. (Univ. Arizona Medical Sch., Tucson, Ariz. 85724); Schneider, M. J. *Nature* 256(5517):500-502; 1975.

Experiments were conducted to determine whether a single hyperthermic treatment could induce thermotolerance in HeLa cells, and to investigate the development of thermotolerance. *In vitro* colony formation was taken as a measure of survival. Thermal doses were administered to exponentially growing cells by immersion of the culture flasks in a water bath at 44 C for up to 3.5 hr. Survival decreased exponentially as a function of time, even when survival was less than 0.1%. There was no shoulder on the survival curve, implying that HeLa cells

did not accumulate sublethal hyperthermic damage. Two-dose experiments were conducted to test for the recovery of HeLa cells from sublethal damage; cell survival increased with increasing incubation at 37 C between two thermal treatments of 44 C for 1 hr. When HeLa cells were treated at 44 C for 1 hr, incubated for 2 hr at 37 C, and then given graded thermal doses, no shoulder was evident on the survival curve during four more hours of treatment; however, the sensitivity of the survival response (as measured by the slope) was changed, implying that the increase in survival after between-dose incubation was not recovery from sublethal damage. Second-dose thermal sensitivity after 2 hr at 37 C was reduced by a factor of three. Reduced thermal sensitivity displayed two characteristics: the process(es) of change were not activated at 44 C (the single-dose curve shows no resistant tail when cells were maintained at 44 C for 3.5 hr) and the changed sensitivity became apparent only when the cells were returned to 37 C before reheating (cell survival was inhibited by incubation at 0 C after heat treatment and before incubation at 37 C prior to reheating). The results thus suggest that thermal resistance is induced by the first dose and is dependent on cell metabolism. In HeLa cells, the maximum change in sensitivity occurs 2 hr after the end of the first dose. The cells do not accumulate or recover from sublethal heat damage. Thus, a single hypothermic treatment can induce a transient state of thermotolerance, but cannot produce heritable hypothermic resistance.

6553 A HISTOCHEMICAL METHOD OF DIFFERENTIATING LOWER GASTROINTESTINAL TRACT MUCIN FROM OTHER MUCINS IN PRIMARY OR METASTATIC TUMOURS. (Eng.) Culling, C. F. A. (Univ. of British Columbia, Dept. Pathology, Vancouver, British Columbia, Canada); Reid, P. E.; Burton, J. D.; Dunn, W. L. *J. Clin. Pathol.* 28(8):656-658; 1975.

The periodate-borohydride/potassium hydroxide (KOH)/periodic acid-Schiff (PAS) technique was used to distinguish between mucins secreted by metastases arising from adenocarcinoma of the lower gastrointestinal tract and mucins secreted by normal or malignant cells from other tissues. Formalin-fixed, paraffin-processed blocks from 80 primary adenocarcinomas of the colon (49), rectum (2), stomach (10), small intestine (1), lung (20), breast (3), bile duct (1), and ovary (1) were examined together with 177 blocks of their metastases. In no instance was a metastasis KOH/PAS positive when the primary tumor was negative. With the exception of one gastric tumor, only tumors that had arisen in the cecum, colon, or rectum gave a positive KOH/PAS reaction; and on no occasion did a metastasis from a negative tumor give a positive result. As previously reported, the KOH/PAS effect is due to the presence of O-acetylated sialic acids in epithelial mucins. Apart from a very pale red coloration seen in the liver, normal tissues from sites other than the lower gastrointestinal tract also did not stain by the periodate-borohydride/KOH/PAS technique. This technique should be useful in determining

the site of the primary tumor when it is in doubt, and in distinguishing between adenocarcinoma of the lower gastrointestinal tract and metastatic primary adenocarcinoma of the lung.

- 6554 AGROGIN 84 SENSITIVITY: A PLASMID DETERMINED PROPERTY IN *AGROBACTERIUM TUMEFACIENS*. (Eng.) Engler, G. (Laboratorium voor Genetica, Rijksuniversiteit Gent, Ledeganckstraat, 35 B9000 Gent, Belgium); Holsters, M.; Van Montagu, M.; Schell, J.; Hernalsteens, J. P.; Schilperoort, R. *Mol. Gen. Genet.* 138(4):345-349; 1975.

Agrocin 84 sensitivity was investigated as a possible plasmid determined property in *Agrobacterium tumefaciens*. Oncogenic, bacteriocin-sensitive strains *A. tumefaciens* strain C58 and B6S3 and Kerr 14 were used. The bacteriocinogenic strains were: *A. radiobacter* S1005, *A. tumefaciens* 396, and *A. radiobacter* 84. Oncogenicity tests, electron microscopic visualization of plasmid DNA, tests for the production of an sensitivity toward agrocin were the basic procedural methods. More precise information was rendered through isolation of agrocin-resistant derivatives and through the appearance of agrocin-resistant colonies as a result of curing of the Ti-plasmid by growth at 37 C. Some *A. tumefaciens* strains showed agrocin 84 sensitivity which seemed determined by the presence of a circular plasmid DNA (Ti-plasmid). Strain C58 was agrocin 84-sensitive, while all Ti-plasmid derivatives were resistant. In growth experiments, the kinetics of appearance of nononcogenic cells and of agrocin 84-resistant cells were identical. The authors conclude that the genes determining agrocin sensitivity are not essential for tumor-inducing ability since all oncogenic, plasmid harboring, *A. tumefaciens* strains are not sensitive to agrocin 84.

- 6555 LOSS OF ABILITY TO SYNTHESIZE COLLAGEN IN FIBROBLASTS TRANSFORMED BY ROUS SARCOMA VIRUS. (Eng.) Levinson, W. (Univ. California Medical Center, San Francisco, Calif. 94143); Bhatnagar, R. S.; Liu, T.-Z. *J. Natl. Cancer Inst.* 55(4):807-810; 1975.

The relationship between behavioral changes in cells transformed by Rous sarcoma virus (RSV, strains: Bryan high titer, Schmidt-Ruppin, and B-77) and the ability of the cells to synthesize collagen was studied in primary chick embryo fibroblasts. The cells were infected with 3 ml tissue culture stock containing 3×10^5 focus-forming U RSV/ml, incubated in medium containing 1.5 μ Ci 3 H-3,4-L-proline/ml (4.8 Ci/mM), dialyzed overnight against cold running tap water and assayed for total radioactivity incorporated and total protein. The fraction of total radioactivity appearing as hydroxyproline was taken as a measure of collagen synthesis. At 24 and 48 hr, synthesis was approximately 50% of normal levels; after 72 hr synthesis was less than 15%. This decrease was not due to decreased prolyl hydroxylase because the level of this enzyme in transformed cells was four times higher than in uninfected cells. It is possible that the cells failed to synthesize col-

lagen polypeptides. Because viral transformation reduces intracellular cyclic AMP concentrations, dibutyryl cyclic AMP and/or theophylline was added (10^{-3} M for 4 or 24 hr), but these agents failed to restore collagen synthesis. These results are contrary to previous findings with other viruses (polyoma, simian virus 40, and Kirsten sarcoma virus).

- 6556 A NITROXIDE-STEROL DERIVATIVE POTENTLY MODIFIES CHOLESTEROL BIOSYNTHESIS BY NORMAL AND NEOPLASTIC GUINEA PIG LYMPHOCYTES. (Eng.) Philippot, J. R. (Tufts New England Medical Center, 171 Harrison Ave., Boston, Mass. 02111); Cooper, A. G.; Wallach, D. F. H. *Biochim. Biophys. Acta* 406(1):161-166; 1975.

The action of 17 β -hydroxy-4',4'-dimethylspiro-[5 α -androstan-3,2'-oxazolidin]-3'-yloxy] was compared with that of cholesterol and 25-hydroxycholesterol on the sterol biosynthesis of normal guinea pig lymphocytes and L2C leukemic guinea pig cells *in vitro*. L2C cells synthesized cholesterol at a 40-fold greater rate than normal cells. Equilibrium (18 hr) with lecithin or lecithin-cholesterol liposomes, respectively, enhanced or suppressed sterol manufacture by normal lymphocytes, but did not influence sterol production by L2C cells. In contrast, over 5×10^9 molecules/cell of 17 β -hydroxy-4',4'-dimethylspiro-[5 α -androstan-3,2'-oxazolidin]-3'-yloxy], drastically inhibited sterol production by both normal and leukemic cells (maximum within two hours). At less than 5×10^9 molecules/cell, this sterol stimulated cholesterol synthesis. 25-Hydroxycholesterol at low concentrations ($<5 \times 10^9$ molecules/cell) also stimulated sterol manufacture, whereas high concentrations were also inhibitory in both cell types.

- 6557 HORMONAL IMBALANCE IN BREAST CANCER. (Eng.) Deshpande, N. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England). *J. Steroid Biochem.* 6(5):735-741; 1975.

The relation of adrenal steroidogenesis in the responsiveness of patients with metastatic breast cancer to endocrine ablation was investigated using both perfusion of the gland *in situ* and continuous peripheral infusion of pregnenolone. The ability of primary breast tumors to synthesize hormones and thus become independent of the hormonal environment was also investigated by the perfusion of the human breast *in situ* and incubation of the neoplasm *in vitro*. The production rate (calculated as the product of the metabolic clearance rate and the plasma concentration of the compound) of pregnenolone was estimated in early or advanced breast cancer patients and noncancerous controls by a continuous infusion technique. There were no significant differences in the metabolic clearance rate, plasma concentration or production rate of pregnenolone in these categories. Unresponsive patients converted a smaller proportion of pregnenolone to androgen (dehydroepiandrosterone) relative to cortisol. The differences in the relative rates of synthesis were not due to abnormalities in the production or metabolic clearance rate of the precursor. In a second series of experiments, women

with primary breast cancer underwent mastectomy. The breast was infused and tumors were homogenized in sucrose, centrifuged, and the supernatant incubated with NADPH or NAD⁺. The reaction was stopped by the addition of alcohol and the steroids separated by paper chromatography. There was no conversion of cholesterol to pregnenolone, 17 α -hydroxypregnenolone to dehydroepiandrosterone, 17 α -hydroxyprogesterone to androstenedione, androstenedione to estrone, testosterone to estradiol or estradiol to estriol *in vitro*. The same substrates also failed to show any metabolism in perfusion of the human breast *in vivo*. Two NAD⁺-linked 3 β -hydroxysteroid dehydrogenase complexes (pregnenolone to progesterone and dehydroepiandrosterone to androstenedione) were detected both *in vivo* and *in vitro*. The author concludes that human breast tumors have a limited biosynthetic capability. Their dependence on a continuous supply of precursors suggests that the tumor plays a minor role in overall steroidogenesis.

6558 STEROID HORMONE RECEPTORS IN HUMAN BREAST CANCER AND THE CLINICAL SIGNIFICANCE.

(Eng.) Maass, H. (Dept. Obstetrics and Gynecology, Univ. Hamburg, Hamburg 20, West Germany); Engel, B.; Trams, G.; Nowakowski, H.; Stolzenbach, G. *J. Steroid Biochem.* 6(5): 743-749; 1976.

Estrogen- and androgen-receptors were determined in human breast cancer tissue by several techniques and the results compared to clinical findings. Methods used for the determination of specific estrogen binding included uptake-competition, agar gel electrophoresis, charcoal adsorption, and hydroxyapatite column assay. In primary breast cancers estrogen receptors were detected in 50 to 60% of the cases and in 35-40% of metastatic tissue. The number of binding sites was 90 femtomol/mg tissue protein. Androgen-receptors were found in 20% of the primary breast cancers and 10% of metastases. There was no correlation between the presence of steroid hormone receptors and menopausal status, histological type of tumor, or cancer-free interval. The content of spare estrogen receptors decreased with increasing serum estradiol levels. Previously published evidence that patients lacking estrogen receptors in their tumor tissue have a very small chance to respond to any kind of endocrine treatment was confirmed by this study. In receptor-negative cases only 19 of 282 cases developed a favorable response compared with 162 of 298 receptor-positive and 8 of 20 borderline cases. The authors conclude that in receptor-negative patients, endocrine ablation procedures, especially adrenalectomy, should be avoided.

6559 ANDROGENS IN POSTMENOPAUSAL BREAST CANCER: EXCRETION, PRODUCTION AND INTERACTION WITH ESTROGENS. (Eng.) Thussen, J. H. H. (Univ. Hosp., State Univ., Catharijnesingel 101, Utrecht, Netherlands); Poortman, J.; Schwarz, F. *J. Steroid Biochem.* 6(5):729-734; 1975.

The role of androgens and estrogens was investigated in postmenopausal breast cancer patients. No dif-

ferences were found in the urinary excretion of estrone and of estriol (both determined by gas chromatography) between 41 primary mammary cancer patients and 48 normal postmenopausal women, representative of the normal population. A significantly lower excretion of 11-deoxo-17-ketosteroids (11-DOKS) was found in the patients. Because 11-DOKS in postmenopausal women arise mainly from three secretory products and estrogens are mainly derived from peripheral conversion of androstenedione to estrone, production rates of dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS) and androstenedione and the conversion of androstenedione to estrone were estimated. No significant difference was found between the two groups for the blood production rate of androstenedione, or for its conversion to estrone. The urinary production rate of DHEAS was lower in the selected breast cancer patients compared to normal controls. The DHEA production rate was also lower, but statistical significance was not achieved. The hypothesis was tested that DHEAS, DHEA or one of their metabolites might interfere with the binding of estradiol to its specific receptor. From the results of an *in vitro* incubation study of receptors from human myometrial and mammary tumour tissue with several steroids, evidence was obtained that the estradiol binding was inhibited, in a molar concentration ratio not far beyond the physiological range, by 5-androstene-3 β ,17 β -diol, a steroid closely related to DHEA. If these *in vitro* findings can be applied to *in vivo* conditions, it is conceivable that androstenediol is a regulating agent of estrogenic action at the cellular level.

6560 TISSUE SPECIFICITY OF THE EPIDERMAL CHALONES. (Eng.) Nome, O. (Oslo Univ., Inst. Pathology, Rikshospitalet, Oslo 1, Norway). *Virchows Arch. [Zellpathol.]* 19(1):1-25; 1975.

The tissue specificity of some chalones, with special emphasis on the chalones found in keratinizing epithelia, was evaluated *in vivo*. The epidermis, the epithelium of the forestomach, and the epithelium of the crypts of jejunum and colon of hairless mice were chosen as an assay system because they represent steady state systems with a well defined proliferating pool. The stathmokinetic method was used to estimate the effects of aqueous extracts of skin, forestomach, glandular stomach, lung, kidney, liver, spleen, and striated muscle on mitotic rate. Autoradiography and liquid scintillation counting were performed to measure the effect of the extracts of skin, forestomach, glandular stomach, and small intestine on DNA synthesis. Five milligrams of skin extract inhibited the mitotic activity of the epidermis (70%) and the forestomach (25%) three hours after ip injection. An inhibiting effect on the epithelial cells of the crypt of jejunum and colon was statistically insignificant. Five milligrams of forestomach extract inhibited the mitotic activity of the epidermis (58%) and of the forestomach (44%). The effect on the jejunum and colon was insignificant. The results support the concept of tissue specificity of the G₂ factor (M chalone) in keratinizing epithelia, regardless of

their ectodermal or endodermal origin. It cannot be excluded that epidermis and forestomach each have their respective organ-specific chalones because the effect was most pronounced in the organ from which each extract was made. Both skin and forestomach extracts (10 mg) inhibited the incorporation of tritiated thymidine (3HTdr) into DNA (pulse labeling) of epidermis and forestomach eight hours after ip injection. No effect was found on jejunum or colon. This supports the concept of tissue specificity of the G₁ factor (S chalone) in keratinizing epithelia. Glandular stomach extract (5 mg) inhibited the mitotic count of epidermis and forestomach, but did not show any depression of the incorporation of 3HTdr into DNA of the same organs. No effect was found in jejunum or colon. No statistically significant inhibition of the mitotic count was found in any of the assay systems after ip injection of 5 mg of extracts made from lung, liver, kidney, spleen or striated muscle, respectively. The results support the hypothesis that squamous cell epithelia produce and contain inhibiting substances (chalones) that act specifically on the progenitor cells in keratinizing epithelia.

- 6561 CLONAL GROWTH OF HAMSTER FREE ALVEOLAR CELLS IN SOFT AGAR. (Eng.) Lin, H.-S. (Washington Univ. Sch. Medicine, St. Louis, Mo. 63110); Kuhn, C.; Kuo, T.-T. *J. Exp. Med.* 142(4): 877-886; 1975.

Free alveolar cells obtained by bronchial lavage from healthy unstimulated male Syrian hamsters were tested for their ability to form colonies in soft agar. The cells were cultured at 37 C in a humidified incubator in 10% CO₂ in air. The medium contained 10% (vol/vol) baby hamster kidney-cell-conditioned medium, 10% fetal calf serum, and 5% horse serum. Colonies were defined as cell aggregates containing more than 50 cells. Every bronchial washing tested contained colony-forming cells. The average plating efficiency was 8.1% (2.4-18.3%). Alveolar colony-forming cells were characterized by having a long initial lag period (4-8 days), and only mononuclear phagocytes were found in the colony; these cells thus resemble peritoneal colony-forming cells. Medium conditioned by baby hamster kidney cells or other cells was required for the initiation and maintenance of their growth. Alveolar cells from normal C3H/He mice and Wistar rats also formed colonies under appropriate culture conditions.

- 6562 MATURATION AND DIFFERENTIATION OF B16 MELANOMA CELLS INDUCED BY THEOPHYLLINE TREATMENT. (Eng.) Kreider, J. W. (Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa. 17033); Wade, D. R.; Rosenthal, M.; Densley, T. *J. Natl. Cancer Inst.* 54(6):1457-1467; 1975.

The effects of theophylline on the maturation, differentiation, cAMP level, and the proliferative and tumorigenic capacity of B16 melanoma cells were characterized *in vitro* and *in vivo*. Within 12 hr after 1.0 mM theophylline was added to growing cultures, the number of cells incorporating tritiated thymidine (3H-TDR) and the rate of uptake of 3H-

TDR into DNA were significantly reduced. The number of cells in control cultures increased 24-fold in 7 days, whereas theophylline-treated cultures increased only 6-fold. Control cells showed an approximately symmetrical distribution of silver grain counts with an average count of 49/cell, whereas the theophylline-treated cells had a marked lower distribution with an average grain count of 37/cell (modal value between 10 and 20 grains/nucleus). The cAMP content of B16 cells treated with 1.0 mM theophylline for 2 days showed a cAMP content of 6.2 ± 0.5 pmoles/ml cell volume in the control cells and 10.6 ± 0.6 pmoles/ml cell volume in the control cells in the theophylline-treated cells. There was a progressive decrease in cell number with an increasing duration of exposure (up to four days) to theophylline, while the control remained fairly constant. In a duplicated experiment using mice, control cells produced tumors 1/3-to 3-times larger than cells treated with theophylline in a period of 7 days. The authors conclude that theophylline accelerates the rate at which mature, differentiated melanocytes were produced in cell cultures of B16 melanoma.

- 6563 BIOCHEMICAL CHANGES IN CULTURED FOETAL RAT LIVER EXPLANTS. (Eng.) MacDonnell, P. C. (Harvard Medical Sch., Boston, Mass. 02215); Ryder, E.; Delvalle, J. A.; Greengard, O. *Biochem. J.* 150(2):269-273; 1975.

The functional integrity of fetal Fisher rat liver explants was investigated. The cubed livers of six to eight albino rat fetuses (20 days old) were incubated in medium supplemented with 25 mM NaHCO₃, 100 U of penicillin, 100 µg of streptomycin, 0.25 µg of fungizone/ml of culture medium. Inactivated horse serum and hormone suspensions were added to obtain final concentrations of 10 µg of glucagon/ml the basic culture medium to obtain final concentrations of 10 µM cortisol, 5 µg insulin/ml and 10 µg of glucagon/ml. After 0, 5, 24 and 48 hr the medium was separated from the culture which was homogenized and centrifuged. Analyses were made of protein content and enzyme activity in the supernatant, the pellet, and the medium. In basic medium the soluble protein concentration decreased from 46.6 to 17.4 mg/g after 24 hr and to 5.8 mg/g in 48 hr (a loss of about 60%). The addition of insulin, cortisol and glucagon separately, or in combination with the basic medium had no effect. There was no decrease in the particulate protein content of the explants. The release of malate dehydrogenase was proportional to the release of total soluble protein into the medium. Tyrosine aminotransferase was not lost from the explants indicating that a portion of the cells were capable of retaining their soluble protein. The authors suggest that a system in which only about one-third of the explant cells are capable of continued chemical differentiation is not suitable for studying the mechanisms of spontaneous or induced quantitative increases exhibited by many hepatic enzymes during the late fetal differentiation *in vivo*.

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- DODD, N.J.F.
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- FERNANDEZ-RANADA, J.M.
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- FILIBE, M.I.
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- FISCHER, D.L.
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- FLEISCHMANN, T.
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- FLEISSNER, E.
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- FLIPPEN, J.H.
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- FLORIDI, A.
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FOX, M. 6471*	GAUNT, I.F. 6102	GORAL, J.E. 6132*
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FRANKLIN, H.R. 6091	GEDEON, E.M. 6447*	GOTTLIEB, A.A. 6588*
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FRAUMENI, J.F., JR. 6495	GEHRING, P.J. 6096	GOUEMAND, M. 6386
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FRIANT, S. 6044*	GELBOIN, H.V. 6085, 6148*	GOURDIN, M.F. 6375*
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FRIEDMAN, M.A. 6169*	GERASINA, S.F. 6270*	GRAEVSKAIA, N.A. 6363*
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FRITSCH, R. 6364*	GERHARTZ, H. 6455*	GRAHAM, R.C., JR. 6388
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FUJII, S. 6535	GERWIN, B.I. 6248	GRANNER, D.K. 6520
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FURNER, R.L. 6546	GILDEN, R.V. 6052*	GRASSO, P. 6102
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GAFFER, A. 6154*	GIRALT, M. 6472*	GREENBERG, M.L. 6511*
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HARDY, W.D., JR.
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HESCOX, M.
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HEWETSON, J.F.
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HOWLEY, P.M.
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HSIE, A.W.
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HSU, B.

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HUIGES, H.A.	ITO, A.	JORDAN, J.A.
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HUMPHREYS, E.R.	ITOH, T.	JUNGMANN, R.A.
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HUNG, G.W.C.	IVANOVA, V.D.	KACHRU, P.B.
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6223	6475*	6349*
HUNSMANN, G.	IYENGAR, B.	KAGEYAMA, K.
6238	6412	6304, 6409
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6311	6490	6368*
HUNTER, A.R.	JACKSON, M.A.	KAKUDO, K.
6527	6490	6141*
HURLEY, P.M.	JACKSON, V.	KALAMKARIAN, A.A.
6070	6520	6467*
HURLEY, T.H.	JACOBS, D.S.	KALASHNIKOV, V.V.
6451*	6422*	6365*
HYNES, R.O.	JACOBSON, K.	KALIFAT, S.-R.
6570*	6113	6473*
IANKOVA, G.D.	JAKOWSKI, R.M.	KALLMAN, B.J.
6130*	6302	6325
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6145*	6393	6409
ICHIMURA, S.	JANIAUD, P.	KAMO, I.
6162*	6080	6292
IFUKU, M.	JANISCH-RASKOVIC, W.	KANAEV, S.V.
6444*	6061*	6459*
IGARASHI, H.	JARVI, O.	KANG, Y.-H.
6277*	6037	6595*
IHLE, J.N.	JEEJEEBHROY, H.F.	KANO, M.
6236	6360*	6157*
IIZUKA, T.	JEFFERIS, R.	KAPLAN, A.M.
6162*	6300	6424*
IJUIN, M.	JENSEN, F.C.	KAPLAN, H.S.
6159*	6254	6350
IKUBO, T.	JERNSTROM, P.	KAPOOR, S.K.
6282*	6474*	6490
ILLMENSEE, R.	JESTER, R.	KARELIN, V.P.
6222	6571*	6270*
INNES, E.M.	JEWELL, W.R.	KARMANOVA, N.V.
6480*	6294	6333
INCUE, A.	JICK, H.	KARN, J.
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INOUE, S.	JINNO, K.	KASTENDIECK, H.
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INSEL, P.A.	JCHANSSON, S.	KASUGA, T.
6538	6174*	6213*
IORIO, A.M.	JOHNSON, D.E.	KATAYAMA, I.
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IRIE, K.	JOHNSON, E.M.	KATELY, J.
6372*	6537	6292
IRIE, R.F.	JOHNSON, F.L.	KATORKIN, E.N.
6367*	6105	6392
IRVINE, W.J.	JOHNSON, L.D.	KATSUKI, T.
6154*	6308	6231
IRVING, C.C.	JONES, B.	KATZE, J.R.
6177*	6134*	6251
ISENBERG, I.	JONES, G.W.	KAUPPILA, A.
6064*	6490	6596*
ISHMAEL, D.R.	JONES, J.V.	KAVETSKII, R.

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KULATUNGA, A.
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KUMAR, S.
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KUJO, E.Y.H.
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KUPERMAN, O.
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KUPOKI, T.
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KUZNETSOV, O.K.
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LAPCHENKOV, V.I.
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LAROUCHE, L.
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LARSEN, C.J.
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LASKAS, J.J., JR.
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LASNE, C.
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LAUNOIS, J.-P.
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LAURENCELLE, L.
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LAVRIN, D.H.
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6089	6469*	6432*
LAYARD, M.W.	LEWINSOHN, H.C.	MACDONALD, H.F.
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LAZAROVA, A.	LIEBELT, A.G.	MACDONNELL, P.C.
6545	6084	6563
LE DAIN, M.	LIEBER, M.M.	MACDOUGALL, D.B.
6362*	6260	6170*
LE FUR, J.M.	LIEBERMAN, I.	MACH, J.P.
6478*	6534	6299
LE MAGOUT, M.	LIEBERMAN, M.	MACH, J.-P.
6080	6350	6364*
LEA, M.A.	LIEBERMAN, M.W.	MACH, O.
6519	6018	6225
LEAMAN, D.H., JR.	LILIENFELD, A.M.	MACHADO, E.A.
6325	6487	6352*
LEAV, I.	LILLY, F.	MACHEMER, L.
6400	6267*	6108
LECLERC, J.C.L.	LIN, H.-S.	MACPHEE, A.A.
6378*	6561	6394
LEDNEY, G.D.	LICTTI, G.	MACPHERSON, I.A.
6291	6578*	6242
LEE, B.J., III	LIPOVA, V.A.	MADISON, R.
6382	6421*	6506*
LEE, S.G.	LITTERST, C.L.	MAENZA, R.
6223	6175*	6190*
LEITH, J.T.	LITTLEFIELD, N.A.	MAHER, V.M.
6197	6126*	6208*
LEJEUNE, F.J.	LIU, S.-L.	MAHLUM, D.D.
6387	6112	6204*
LEJONC, J.L.	LIU, T.-Z.	MAKAROV, O.V.
6375*	6555	6365*
LEJONC, J.-L.	LCBANCVA, A.M.	MAKISHIMA, K.
6473*	6594*	6475*
LENK, S.	LOISILLIER, F.	MAKIURA, S.
6512*	6331	6140*
LEONARD, C.	LONGHI, G.	MAKSUMOV, D.N.
6336	6568*	6443*
LEONARD, C.M.	LONGLEY, C.	MALAOWALLA, A.M.
6341*	6351*	6493
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LESCURE, B.	LOWY, D.R.	MALIS, L.I.
6241	6262	6414
LESSER, G.R.	LOZZIO, B.B.	MALLING, H.V.
6289	6352*	6093
LEUTZ, J.C.	LOZZIO, C.B.	MALYSHEV, I.U. I.
6085	6352*	6392
LEVINA, D.S.	LU, A.T.	MANI, N.J.
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LEVINA, N.V.	LUBBERT, H.	MANNICK, J.A.
6151*	6591*	6344*
LEVINE, G.D.	LUBIN, F.	MANNONI, P.
6380*	6043*	6375*
LEVINE, P.H.	LUCAS, A.O.	MANOJLOVIC, N.
6385	6490	6199
LEVINSON, W.	LUCAS, Z.J.	MANS, R.
6555	6303	6521
LEVIS, W.R.	LUEDERS, K.K.	MANSSELL, M.M.
6144*	6357*	6586*
LEVO, Y.	LUMB, J.R.	MANTOVANI, A.
6384	6582*	6286
LEVY, C.C.	LUSTIG, T.M.	MARCINKIEWICZ, C.
6542	6574*	6044*
LEVY, J.A.	LYNCH, W.E.	MARDINEY, M.R., JR.

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MARIAGE, R.
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MARKOVITS, P.
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MARONPOT, R.
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MARRONE, J.C.
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MARSH, J.C.
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MARTIN, M.A.
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MARTINEZ JIMENEZ, J.
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MARTINI, L.
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MARTY, M.
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MARUSYK, R.G.
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MARUYAMA, K.
6272*
MARK, J.N.
6184*
MASSE, R.
6478*
MATSUI, T.
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POLLIACK, A.
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POLLOW, K.
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POUCHELET, M.
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6262	6584*	6121*
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6274*, 6275*	6075	6064*
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6573*	6479*	6124*
TERMAN, D.S.	TPUCKSESS, M.W.	VAN WENT-DE VRIES, G.F.
6318	6122*	6090
TERMINI, T.E.	TSAI, T.	VARGHESE, A.J.
6569*	6499	6101
TERRANOVA, T.	TSESHKOVSKII, M.S.	VASHKINEL, V.K.
6568*	6464*	6459*
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6288	6158*	6365*
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6122*	6548	6522
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6324, 6600*	6282*	6481*
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6431*	6589*	6472*
THOR, O.E.	TUCCI, M.	VEIT, B.C.
6343*	6578*	6285
THRALL, C.	TUCHAIS, C.	VENITT, S.
6521	6512*	6095
THUSSEN, J.H.H.	TUCHAIS, E.	VENKITASUBRAMANIAN, T.A.
6559	6512*	6071
TIOWELL, T.	TUCHIYAMA, H.	VERHULSDONK, C.A.H.
6273*	6444*	6124*
TISCHENKO, M.A.	TUCKER, S.	VERINGA, H.A.
6445*	6435*	6121*
TISDALE, V.G.	TULLIEZ, M.	VIANNA, N.J.
6582*	6473*	6009
TOBIAS, C.A.	TUMYAN, B.G.	VIDALI, G.
6197	6333	6517
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6413	6564*	6596*
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6535	6132*	6266*
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6196	6089	6381
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6156*	6428*	6192*
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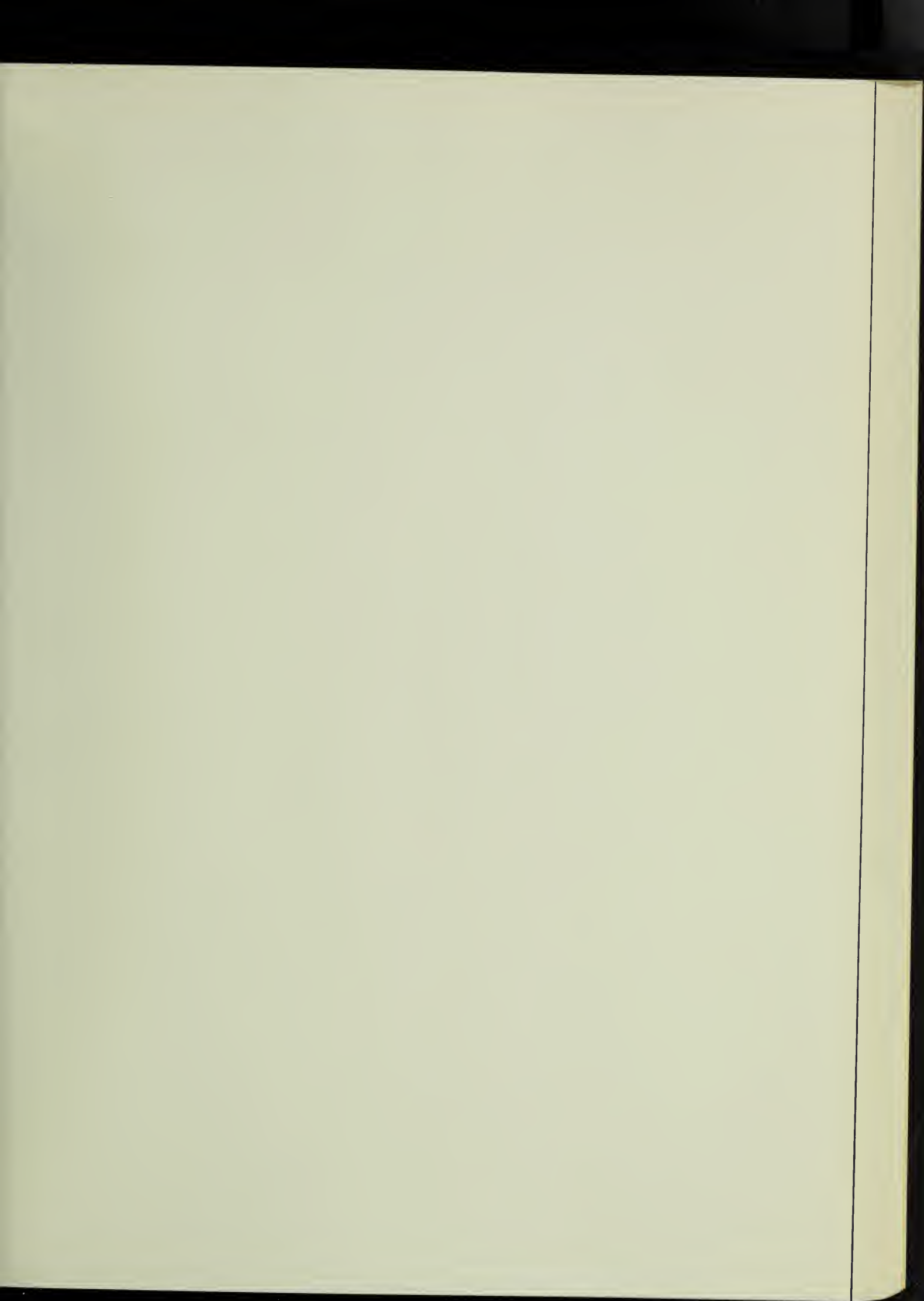
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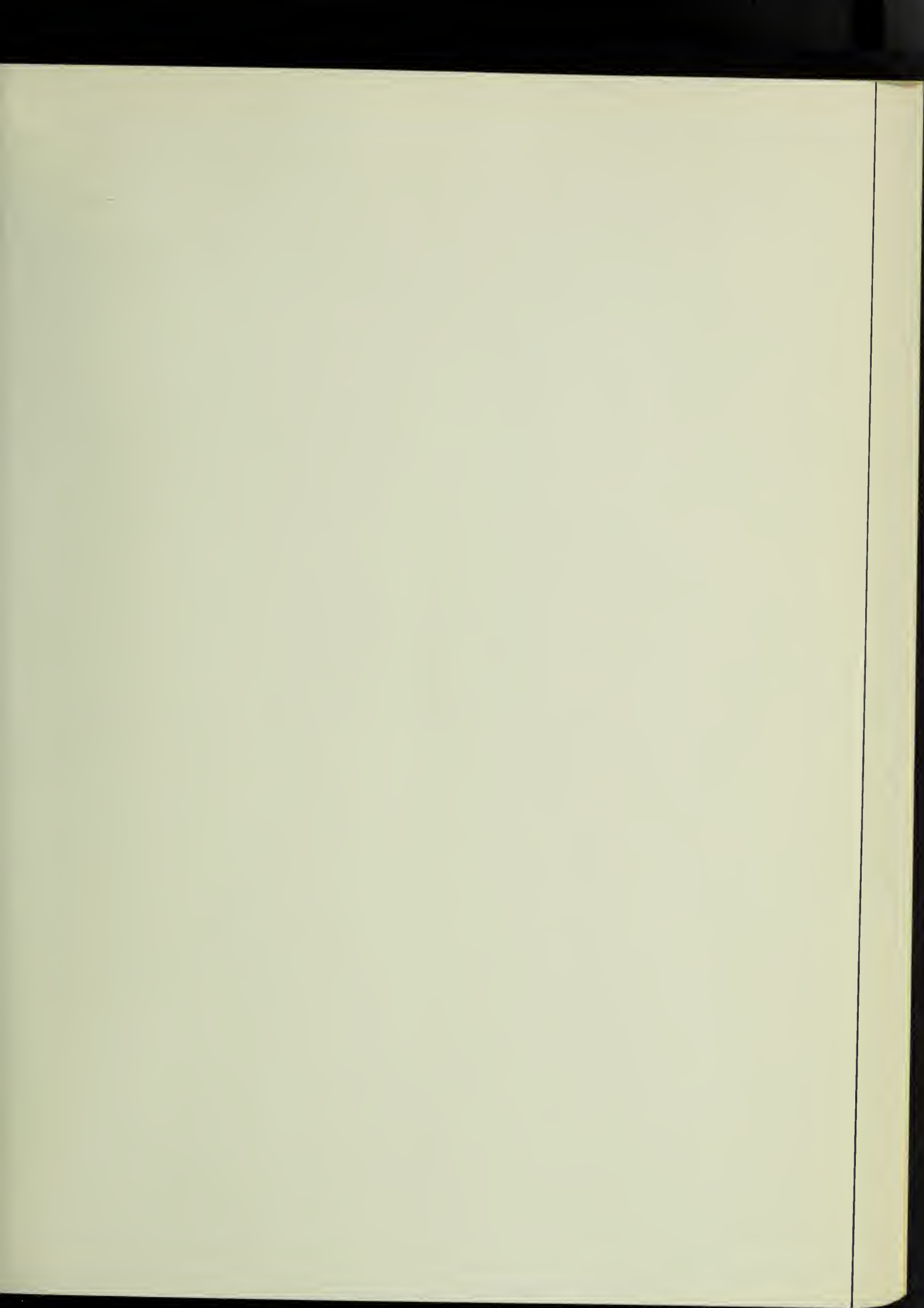
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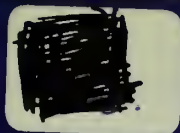
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THE UNIVERSITY OF CHICAGO

CARCINOGENESIS ABSTRACTS

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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

Carcinogenesis Abstracts is normally published monthly. Volume XIII covers the scientific literature published from Jan 1975 through Dec 1975. To increase the usefulness of *Carcinogenesis Abstracts*, Volume XIII, a Wiswesser Line Notation index and a Chemical Abstracts Service Registry Number index have been provided. These indexes reference compounds described in abstracted articles. A cumulative subject, author, CAS Registry Number, and Wiswesser Line Notation index for Volume XIII will be published shortly after the final regular issue.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations found in *Chemical Abstracts Service Source Index*, 1907-1974 Cumulative, are used. New journals are verified in *New Serial Titles* and abbreviated according to *International Standard ISO 833*. An asterisk indicates the author to address (other than the primary) in requesting reprints.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	Ind.	Indonesian
Ara.	Arabic	Ita.	Italian
Bul.	Bulgarian	Jpn.	Japanese
Chi.	Chinese	Kor.	Korean
Cro.	Croatian	Lav.	Latvian
Cze.	Czech	Lit.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
Eng.	English	Por.	Portuguese
Est.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fle.	Flemish	Ser.	Serbo-Croatian
Fre.	French	Slo.	Slovak
Geo.	Georgian	Spa.	Spanish
Ger.	German	Swe.	Swedish
Gre.	Greek	Tha.	Thai
Heb.	Hebrew	Tur.	Turkish
Hun.	Hungarian	Ukr.	Ukrainian
Ice.	Icelandic	Vie.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

A	angstrom(s)	M	molar
ACTH	adrenocorticotrophic hormone	mM	millimolar
ADP	adenosine diphosphate	μ M	micromolar
AMP	adenosine monophosphate	mOsm	milliosmolar
ATP	adenosine triphosphate	mEq	milliequivalents
BCG	Bacillus Calmette Guerin	min	minute(s)
bid	twice daily	mo	month(s)
C	degrees centigrade	MTD	maximum tolerated dose
cal	calorie(s)	N	normal concentration
kcal	kilocalorie(s)	NAD	nicotinamide adenine dinucleotide
cc	cubic centimeter(s)	NADH	reduced nicotinamide adenine dinucleotide
Ci	curie(s)	NADP	nicotinamide adenine dinucleotidephosphate
mCi	millicurie(s)	NADPH	reduced nicotinamide adenine dinucleotide-phosphate
μ Ci	microcurie(s)		
cm	centimeter(s)	ng	nanogram(s) (10^{-9})
CNS	central nervous system	od	once daily
cpm	counts per minute	Pa	ambient pressure
dL	deciliter(s)	PAS	periodic acid-Schiff
mL	milliliter(s)	Pg	picogram(s) (10^{-12})
μ L	microliter(s)	PgEq	picogram equivalent
DNA	deoxyribonucleic acid	po	orally
ED ₅₀	median effective dose	ppb	parts per billion
EDTA	ethylenediamine tetraacetic acid	ppm	parts per million
ESR	erythrocyte sedimentation rate	qid	four times daily
g	gram(s)	qod	every other day
kg	kilogram(s)	QO ₂	oxygen quotient
mg	milligram(s)	R	roentgen(s)
μ g	microgram(s)	RBC	red blood cells (erythrocytes)
Hb	hemoglobin	RNA	ribonucleic acid
hr	hour(s)	sc	subcutaneous
ia	intra-arterial	sec	second(s)
ic	intracerebral	SGOT	serum glutamic-oxalacetic transaminase
icav	intracavitary	SGPT	serum glutamic-pyruvic transaminase
id	intra-dermal	SRBS	sheep red blood cells
ILS	increased life span	TCD	tissue culture dose
im	intramuscular	TCD ₅₀	median tissue culture dose
ip	intra-peritoneal	tid	three times daily
ipl	intrapleural	U	unit(s)
it	intratumorous	mU	milliunit(s)
IU	International Unit	UV	ultraviolet
iv	intravenous	vol	volume
K _m	Michaelis constant	WBC	white blood cells (leukocytes)
LD	lethal dose	wk	week(s)
LD ₅₀	median lethal dose	wt	weight
m	meter(s)	x	times
mm	millimeter(s)	yr	year(s)

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REVIEW

- 6601 *N*-NITROSAMINES IN FOODS. (Eng.) Scanlan, R. A. (Dep. Food Sci. Technol., Oregon State Univ., Corvallis). *Crit. Rev. Food Technol.* 5(4):357-402; 1975.

The formation of nitrosamines in food is reviewed. A number of components, such as thiocyanate ion and formaldehyde, have been shown to accelerate nitrosation, and the use of ascorbate or erythorbate to inhibit nitrosation in foods appears promising. Methods are available for the identification and quantitation at the 1 to 10 parts per billion (ppb) level for approximately 14 volatile nitrosamines. Essentially no sensitive, specific methods are currently available for the analysis of nonvolatile nitrosamines although several approaches look promising. A number of recent reports, using reliable methodology, have identified dimethylnitrosamine and nitrosopyrrolidine, usually at the lower ppb level, in various cured meat products. The occurrence of dimethylnitrosamine has been very sporadic and at present there is no explanation for the randomness. Nitrosopyrrolidine occurs consistently in fried but not in uncooked bacon. The amount formed appears to be directly related to the amount of added nitrite and to the temperature at which the bacon is fried. Dimethylnitrosamine has been reported to occur sporadically at low levels in fish products. The occurrence in samples of raw fish is particularly puzzling and needs further investigation. Nitrosamine in foods is still a problem and will probably require considerably more work to allow satisfactory solutions. The aim for the future must be to determine the extent of nitrosamine occurrence in our foods, in our environment, and to determine the hazard to man from this occurrence. If a hazard exists, steps should be taken to minimize or eliminate the hazard. (197 references)

- 6602 CARCINOGENIC *N*-NITROSO COMPOUNDS. (Eng.) Lijinsky, W. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, Tenn.); Singer, G. M.; Taylor, H. W. *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 44-47.

The occurrence and formation of *N*-nitroso compounds is reviewed. Tumors have arisen in every organ and tissue and from most types of cells in response to treatment of animals with some nitroso compound. The effect varies with the dose and length of treatment and has been changed by altering the physiological state of the organ (i.e. partial hepatectomy). Most types of tumor found in man can be reproduced in experimental animals with *N*-nitroso compounds. *N*-nitroso compounds possess all of the characteristics ascribed to carcinogens of any type. Because nitroso compounds show striking differences between species in the site and type of tumors they induce, it is difficult to relate human cancer to exposure to particular nitroso compounds. Reports of naturally occurring *N*-nitroso compounds are rare; two are streptozotocin and 4-methylnitrosaminobenzaldehyde. The most significant source of nitroso compounds is their formation in the stomach,

a favorable site for nitrosation of secondary and tertiary amino compounds. Nitrosation of secondary amines will occur at neutral pH, particularly if catalyzed by certain carbonyl compounds such as formaldehyde. Ascorbic acid and phenols inhibit the reaction. The formation of nitroso compounds from ingested nitrate has been shown as a factor in carcinogenesis. In order to lessen the tumorigenic potential of long-term human ingestion of amine mixtures the authors propose a reduction in the dietary intake of nitrite. (17 references)

- 6603 DIET AND DISEASE. A PLEA FOR POTATOES. (Eng.) Burkitt, D. P. (Medical Res. Council, London, England). *J. Ir. Coll. Physicians Surg.* 4(4):141-145; 1975.

Dietary factors are proposed to explain the high prevalence of certain diseases in Ireland compared with their low prevalence in many developing countries. These diseases include ischemic heart disease, cancer of the colon and rectum, gallstones, appendicitis, diverticular disease, hemorrhoids, varicose veins, and hiatus hernia. Communities with a low prevalence of these diseases eat large quantities of little refined, relatively fiber-rich, plant foods. One of the main characteristics of areas with a high prevalence of the diseases is the consumption of fiber-depleted carbohydrates, mainly those containing sugar and finely milled flour. By significantly altering intestinal transit times and stool weights, low-fiber diets may play a causative role in these diseases. Small viscid feces resulting from low-fiber diets are related to the raised intracolonic pressures found in diverticular disease and appendicitis, and to the raised intra-abdominal pressures found in hiatus hernia, hemorrhoids, and varicose veins. Cholesterol gallstones may be related to changes in bile acid and cholesterol metabolism effected by fiber-depleted carbohydrate foods. In large intestine cancer, the intestinal stasis and fecal concentrations associated with low-fiber diets may enhance the action of carcinogens resulting from bacterial degradation of bile salts and other fecal constituents. Both epidemiologic and experimental evidence suggest that lack of dietary fiber also may play a major role in the pathogenesis of ischemic heart disease. Since all these diseases are associated with prolonged intestinal transit time and small firm stools, a return to cereal fiber and potatoes is suggested. (27 references)

- 6604 THE METABOLIC ACTIVATION AND REACTIVITY OF CARCINOGENIC AROMATIC AMINES AND AMIDES. (Eng.) Miller, E. C. (Univ. Wisconsin Medical Center, Madison, Wis. 53706); Miller, J. A. *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 3-8.

The metabolic activation of some carcinogenic aromatic amines and amides, and the interactions of the ultimate carcinogens with the target tissues are reviewed. Detailed studies on the metabolism and carcinogenicity of 2-acetoaminofluorene have

served as the basis for many subsequent studies. 2-Acetylaminofluorene is readily N-hydroxylated by rodent livers to the more potent carcinogen N-hydroxy-2-acetylaminofluorene; this metabolite is subject to a variety of enzymatic conversions into electrophilic reactants. Hepatic fluorene derivatives receiving detailed study have included: N-(guanosin-8-yl)-2-acetylaminofluorene and the 2-aminofluorene analogue, N-(deoxyguanosin-8-yl)-2-aminofluorene; N-(deoxyguanosin-8-yl)-2-acetylaminofluorene; and N²-(2-acetylaminofluorene-3-yl)-guanine. Correlative studies have suggested that the sulfuric acid ester of N-hydroxy-2-acetylaminofluorene is the major precursor of the hepatic RNA-bound 2-acetylaminofluorene derivatives. Investigations on the carcinogens 4-acetylaminotransstilbene, 2-acetylaminophenanthrene, and 4-acetylaminobiphenyl have suggested the *in vivo* formation of potent N-hydroxy derivatives and subsequent hepatic sulfotransferase, acetyltransferase, and one-electron oxidation reactions. The esters of N-hydroxy-4-acetylaminotransstilbene, N-hydroxy-2-acetylaminophenanthrene, and 4-hydroxyaminoquinoline react with adenine and cytosine residues to a greater extent than the esters of N-hydroxy-2-acetylaminofluorene. Studies on the hepatic activation of aromatic amines indicate that the hepatocarcinogenic activities of secondary aminoazobenzene dyes appear to depend on their N-hydroxylation and subsequent esterification; activation *via* oxidation to a free radical is also suggested. Investigations on the mechanisms of carcinogenesis reveal ultimate electrophilic metabolites of aromatic amines and amides found to react with DNA's, RNA's, and proteins in the target tissues. Noncovalent interactions and chemical reactions resulting in an altered macromolecule are also suggested; the basic mechanisms of chemical carcinogenesis may be either genetic or epigenetic in nature. (64 references)

- 6605 CANCER AND CHEMICALS. (Eng.) Ferguson, L. N. (California State Univ., Los Angeles). *Chem. Soc. Rev.* 4(2):289-322; 1975.

The chemical aspects of developments in cancer chemotherapy are reviewed and the importance of environmental carcinogens is emphasized. Epidemiologists have estimated that up to 90% of all cancers are produced by environmental factors. Five groups of chemical carcinogens, polycyclic aromatics, biological alkylating agents, aromatic amines and azo-compounds, N-nitroso-amines and -amides, and metallic substances, are described. The four widely used modes of cancer therapy include: surgery, radiation, chemo-, and immunotherapy; approaches such as electrosurgery, chemosurgery, cryosurgery, and thermotherapy are under investigation. Ten human cancers are highly responsive to chemotherapy and 50% of patients affected by them achieve normal life expectancy. Longer remissions can be achieved through chemotherapy; however, this does not apply to the major cancer killers, i.e., breast, colon, or lung cancer. Drugs currently in use are not highly effective against old tumors with low DNA synthesis rates (e.g., colon and lung cancers). Some of the approaches currently used as guidelines

for potential antitumor agents are presented. Quantitative structure-activity relationships include ranking substructure contributions to biological activity by statistical methods and correlating physiochemical properties of a family of molecules with their bioactivity. The target-specific approach uses as a guide the structure of compounds known to localize in certain body sites or having a specific biological activity. Another technique deals with seeking similar molecular structure fragments among compounds exhibiting some common property (e.g., the O-N-O triangulation of some common nonalkylating antileukemic drugs). Drugs which form intercalations between DNA base pairs and inert or nontoxic agents that are converted by enzymes or radiation into cytotoxic substances at the tumor site are also being investigated. The search for anticancer agents continues in agricultural and marine plants and animals. Generally, the rational design of cancer drugs is based on exploitable biochemical differences between normal host and invading cancer cells. Two recent strategies for more effective use of the available drugs include the administration of several drugs in succession or an early combination of chemotherapy with surgery and/or radiation therapy. The authors conclude that a cancer breakthrough will require a better understanding of the mechanism of action of antitumor agents, and indicate a need for biochemical mechanistic studies of carcinogenesis and cytotoxic actions. (165 references)

- 6606 NEGLIGIBLE RISKS TO HEALTH. (Eng.) Knox, E. G. (Dept. Social Medicine, Univ. Birmingham, Birmingham, England). *Community Health (Bristol)* 6(5):244-251; 1975.

The problem of determining negligible risk in connection with such situations as the use of drugs, diagnostic procedures, operations, and radiation therapy is discussed. Three basic approaches seem to be used to define such risks: 1) the principle of nonmeasurability, 2) the principle of statistical distribution, and 3) the principle of accustomed risk. Upon examination, each of these principles was found inadequate. A behavioral principle for determining negligible risk is proposed which states that a situation may be regarded as safe, and the associated hazards negligible, if reasonably informed and experienced people, when offered the option, in fact disregard the risk. The level must be determined by observing how they behave. The accurate identification of risks which people willingly neglect requires observation of a set of situations in which the risks are set against negligible benefits. Behavioral studies in this field need to investigate the attitudes of persons sufficiently informed toward exhibiting "responsible" reactions. Examples from various fields (compulsory car insurance, flight insurance, compulsory fitting of seat belts in cars) and especially medical examples (discontinuance of small pox vaccinations in infants, diagnostic use of radiology in pregnant women, use of the contraceptive pill) lead to the conclusion that a risk of about 10^{-5} consequent upon a single decision is somewhere near the level below which concern ceases; that is, the level at

which a procedure is considered safe. One of the problems of seeking a behaviorally-based definition of negligibility arises from the variety of situations in which responses may be observed, and the various qualities of risk for which a numerical specification is attempted. Such situations offer scope for contradiction and for inconsistency of approach, and suggest that the same numerical level of risk may be assessed as negligible in one operational situation but not in another. It is emphasized that the credentials of the behavioral approach for defining levels of negligibility are not dependent upon the consistency of the results. Consistency is the objective rather than the basis of the behavioral standard. Its main purpose is to display variations of attitude in different circumstances and thereby to encourage a greater degree of uniformity than at present exists. (12 references)

- 6607 ESTIMATING "SAFE" LEVELS, A HAZARDOUS UNDERTAKING. (Eng.) Mantel, N. (Biostatistics Cent., George Washington Univ., Bethesda, Md.); Schneiderman, M. A. *Cancer Res.* 35(6):1379-1386; 1975.

Various problems beset the question of identifying chemical carcinogens in the environment or setting permissible levels for potential carcinogens. Issues arising are cost-benefit questions, existence of thresholds, appropriate experimental designs, how to extrapolate to man, results from tests on laboratory animals, etc. Certain approaches implicitly involve use of a double standard, with much more stringent measures taken when clearer evidence of carcinogenicity is found. Such double standards may discourage careful testing of carcinogens as this could more probably lead to imposition of the stricter measure. Even-handed application of an extrapolation procedure for setting "safe" levels could avoid this difficulty and would encourage more adequate testing. The Mantel-Bryan procedure uses one rule of extrapolation for all circumstances and can set "safe" levels from any size experience; it avoids the need for demonstrating the existence of threshold levels, does not attempt to categorize an agent as absolutely safe or unsafe at any dose, and does not require conformity to a fixed experimental protocol. The need for laboratory testing to be at high or moderately high levels is explained and the futility of "mega-mouse" experiments at very low dose levels is indicated. A surface-area rule for extrapolating dose levels from laboratory animal to man is suggested, but this is indicated to lead approximately to direct equivalence when dose levels are expressed as dietary concentrations. (15 references)

- 6608 ESTABLISHMENT OF THE PRIMARY EFFECT IN EXPERIMENTS WITH CHEMICAL CARCINOGENS. (Rus.) Olenov, Yu. M. (Lab. Genet. Tumor cells, Inst. Cytol. Acad. Sci. USSR, Leningrad, USSR). *Vopr. Onkol.* 21(4):63-74, 1975.

Cancer is discussed as a change in the level of differentiation in cells as manifested in changes in antigen production (e.g. tissue specific antigen), enzyme synthesis, and ectopic hormone pro-

duction. Literature on the effects of dimethylaminoazobenzene, dimethylnitrosamine, CCl₄ and polycyclic hydrocarbons on cell immunology and metabolism and tissue morphology, and of the functional state of the body on carcinogenesis is reviewed. The phenomenon of spontaneous regression in a cancer cell population with the appearance of a "third type of cell", neither neoplastic nor normal, and the implications of this phenomenon for oncology are discussed. Karyological studies of cell cultures, cancer cells and the "regressed" cells are also reviewed. (85 references)

- 6609 CLINICAL MANAGEMENT OF WORKERS EXPOSED TO VINYL CHLORIDE AND POLYVINYL CHLORIDE. (Eng.) Johnson, C. A. (Goodyear Tire Rubber Co., Akron, Ohio). *Ann. N.Y. Acad. Sci.* 246:313-319, 1975.

A program designed to prevent occupational disease in vinyl chloride and polyvinyl chloride (PVC) workers is reviewed. Three requirements of a reliable medical surveillance program are mentioned: 1) the program must be capable of detecting physiological or biochemical alteration prior to the development of disease; 2) it must be capable of detecting disease before significant irreversible impairment develops; and 3) if physiological or biological alteration occurs, or if disease develops and the worker is removed from further exposure to prevent progress of the disease to a disabling or life-threatening state, continued medical surveillance is needed to detect evidence of reversibility as a result of the removal from exposure or the effectiveness of other appropriate therapeutic measures. An extensive periodic medical surveillance program developed for workers involved in the PVC resin production operations of Goodyear Tire and Rubber Co. consists of the following: 1) comprehensive medical history, 2) examination by a physician, 3) posterior and anterior view of the chest, 4) x-ray of both hands to detect early vascular changes in the distal phalanges in PVC workers, 5) pulmonary function tests, and 6) clinical laboratory procedures consisting of: hemoglobin and hematocrit determination, WBC count and differential, a platelet count, a blood chemistry profile, a routine urinalysis, and a urine cytology. The examination program was explained to union representatives and approved by union officials. The worker is informed of the results of the examination which are made available to any physician designated by the worker. It is concluded that an effective prevention program must include the cooperative efforts of the toxicologist, the process engineer, the industrial hygienist, the physician, and the worker. A discussion of the problem of vinyl chloride and PVC in the work environment follows. (No references)

- 6610 CURRENT CONCEPTS OF CHRONIC BENZENE TOXICITY. (Eng.) Snyder, R. (Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, Pa.); Kocsis, J. J. *CRC Crit. Rev. Toxicol.* 3(3): 265-288; 1975.

Aspects of chronic benzene toxicity are reviewed,

including chronic benzene toxicity in humans, animal studies on chronic benzene toxicity, the relationship between benzene toxicity and leukemia, immunological effects of benzene, benzene metabolism *in vivo* and *in vitro*, and the relationship between metabolism and toxicity. Chronic benzene exposure in man leads to a progressive disease in which bone marrow function becomes increasingly depressed until it ceases to function in the production of normal blood cells. In benzene-treated animals, DNA synthesis is reduced in bone marrow either because of inhibition of enzymes involved in DNA synthesis or because reduced incorporation of thymidine into DNA occurs at some point in the cell cycle. Although epidemiological studies among workers in industries where benzene exposure is a hazard have failed to demonstrate a correlation between the incidence of leukemia and benzene exposure, many individual cases of leukemia have been linked to benzene. In benzene intoxication, serum complement levels, immunoglobulin G (IgG) and IgA are decreased while IgM levels are slightly higher. These observations may explain why benzene-intoxicated individuals readily succumb to infection and the terminal event in severe benzene toxicity is often an acute, overwhelming infection. Alterations in immunological function may also play a role in the development of acute leukemia resulting from benzene intoxication. Benzene is hydroxylated by the microsomal mixed function oxidase to phenol and other hydroxylated benzene derivatives probably via an epoxide intermediate. In several studies, the effect of benzene on a parameter of bone marrow activity was correlated with the rate of benzene metabolism either *in vivo* or *in vitro* using liver preparations. Since benzene toxicity is manifested in the bone marrow rather than the liver, it is argued either that a toxic metabolite travels from the liver to the bone marrow or that the metabolite is formed in the bone marrow. It is suggested that the most profitable tissue for studying the role of benzene metabolism in relation to toxicity is the bone marrow, possibly using the techniques of tissue culture. (220 references)

- 6611 TOBACCO RADIOACTIVITY AND CANCER IN SMOKERS. (Eng.) Martell, E. A. (Nat'l. Center for Atmospheric Res., P. O. Box 3000, Boulder, Colo. 80303). *Am. Sci.* 63(4):404-412; 1975.

Processes leading to the formation of insoluble radioactive smoke particles, the possible cancer risks, and other health consequences of such alpha-emitting particles are reviewed. The formation of insoluble cigarette-smoke particles highly enriched with ^{210}Po is discussed in detail. The presence of ^{226}Ra in tobacco soils, and the enrichment of ^{210}Po on small Aitken particles, on tobacco trichomes, and in insoluble smoke particles are especially considered. Studies of the possible biological significance of such alpha-emitters have dealt with the localization in lung tissue and the mutagenic effects of alpha radiation. Chromosomal structural changes resulting from alpha interactions are directly proportional to the number of alpha interactions, independent of the dose rate, and conform to a two-mutation sequence of events. Studies of the organ

distribution of alpha-emitting ^{210}Po have shown that tissue sites of known or expected accumulation include all the internal organ sites at which human cancers are known to occur. While the accumulation of insoluble particles in the lung tissue of both smokers and nonsmokers has been found to be uniformly distributed, the lung tissue of cigarette smokers has an excess alpha-irradiation dose compared to that of nonsmokers. There is also evidence that atherosclerosis plaques may be due to the mutagenic effects of alpha activity. While various chemical constituents of tobacco smoke are possible carcinogens, it is postulated that insoluble alpha-emitting particles are the effective carcinogenic agents. Long-term radiation damage may be the prime contributor to degenerative diseases of the cardiovascular and renal systems. (38 references)

- 6612 ENZYMATIC REPAIR OF DNA DAMAGE IN MAMMALIAN CELLS. (Eng.) Lett, J. T. (Dept. Radiology and Radiation Biology, Colorado State Univ., Fort Collins, Colo.). *Proc. Int. Cancer Congr. 11th.* Vol. 5 (*Surgery, Radiotherapy and Chemotherapy of Cancer*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 98-104.

The formation and subsequent fate of DNA strand-breaks in irradiated mammalian cells is reviewed. Both alkaline environments and low doses of radiation appear to degrade mammalian DNA in a nonrandom fashion, through a series of DNA components of decreasing size, until single-stranded DNA molecules of about 165S appear. This led to the formulation of a working model of the DNA structure in the mammalian chromosome which is based upon linked arrays of molecules of size 165S. This model can be used to interpret the strand-break rejoining mechanisms in irradiated cells. DNA single-strand breaks are induced with similar efficiencies by x-rays in proliferating cultures of mammalian cells at all stages of the cycle. The same results are obtained with nondividing cells locked in G_0 *in situ*. The values for the strand-breaking efficiencies fall in the range 30-70 eV/strand break. Values of 1000-3000 eV have been obtained per double-strand break. Problems involved in correlating the oxygen enhancement ratio for cellular x-ray survival to the production of DNA single- and double-strand breaks have not been solved. Studies of DNA single strand-break rejoining at the subunit level indicate that following aerobic irradiation at least 95% of the strand-breaks are rejoined. Recent evidence indicates that about 10% of the breaks produced by x-irradiation under extreme hypoxia are not rejoined. It is expected that distinction between the consequences of aerobic and anoxic irradiations may soon be forthcoming. An investigation carried out with DNA species bigger than the 165S molecules has shown a cell-cycle dependence of strand-break rejoining in heavily x-irradiated (22 krads), synchronous populations of Chinese hamster ovary cells. Studies with nondividing cells of the central nervous system which were locked in G_0 *in situ* support the contention that at least two strand-break rejoining mechanisms operate in x-(γ)-irradiated mammalian cells: one of these mechanisms reconstitutes the 165S mole-

cles and the other links the reconstituted subunits together and restores the overall DNA structure. Other investigations have indicated that a critical temporal event in the molecular mechanisms underlying recovery from sublethal radiation damage may relate to the onset of the "linker rejoining" mechanism. Double-strand break rejoining was investigated in Chinese hamster ovary cells irradiated with γ -rays or α -particles. It was found that the double-strand breaks induced by γ -rays are completely rejoined following doses up to 50 krads, while the double-strand breaks induced by α -particles are incompletely rejoined (up to 80%) at all doses. It is concluded that it is not gross DNA damage which is related to cell lethality but rather DNA damage of specific types or at specific sites which is crucial. (25 references)

- 6613 GENETIC RISKS FROM MEDICAL RADIATION. (Eng.) Seelentag, W. (World Health Organization, Geneva, Switzerland). *WHO Chron.* 29(4): 117-122; 1975.

Reports of the United Nations Scientific Committee on the Effects of Atomic Radiation concerning genetic risks from medical radiation are presented. Genetic effects, determined by the total radiation dose received by the gonads, appear only in future generations; therefore, the "child expectancy" factor, which depends on the age of the irradiated person, must be taken into account for calculations of the genetically significant dose (GSD). A 1972 report revealed that the average radiation dose from natural exposure for the world population is 100 mrad/person/yr; in most countries, the genetically significant radiation from the X-ray diagnostic procedures amounts to 10-50% of the natural background radiation. Medical radiation exposure of patients contributes most to the exposure of whole populations; the contributions from the exposure of medical staff and occupational exposures are much smaller. The GSD from diagnostic X-ray examinations and mass chest surveys varies between countries depending on the technique, technical factors, protection from radiation, times exposed per examination, and the actual radiation dose measured at the gonads during the different types of X-ray examinations. For example, radiographs of the lung without proper collimation of the beam may result in the same genetic exposure as 150 radiographs carried out with proper technique; for radiographs of the abdomen, proper collimation can reduce the gonad dose by a factor of 30. The author concludes that physicians and technicians must be properly trained in radiological methods and planning radiation protection so that the medical uses of ionizing radiation will be as safe as possible for the present and future generations. In addition, *A Manual On Radiation in Hospitals and General Practice* is reviewed. (6 references)

- 6614 CHEMICAL NATURE OF LESIONS PRODUCED IN DNA BY IONISING RADIATION. (Eng.) Hagen, U. (Institut für Strahlenbiologie, Kernforschungszentrum Karlsruhe, D 75 Karlsruhe, Postfach 3640, West Germany). *Proc. Int. Cancer Congr.* 11th. Vol. 5 (*Surgery, Radiotherapy and Chemotherapy of*

Cancer). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 77-82.

Ionizing radiation-induced DNA damage is discussed with emphasis on changes in the macromolecular structure of DNA, radiation damage to the nucleotide bases, and configuration of the strand break. Breaks of the nucleotide chain, crosslinks, and a rupture of the hydrogen bonds between the strands of the double helical DNA are the predominant radiation effects. In aqueous solution, radiation causes breaks of a single nucleotide chain, whereas irradiating DNA in dry form results in the rupture of both strands. The frequency of strand breaks, both *in vivo* and *in vitro*, is considerably enhanced when the radiation is performed in the presence of oxygen rather than under anaerobic conditions. Thymine is twice as sensitive as the other DNA bases to destruction by ionizing radiation. In total, about four bases are destroyed per single strand break formed. The secondary structure of DNA influences base destruction by radiation, in double stranded DNA, much less thymine is destroyed than in nucleotide mixtures. (It is pointed out that only thymine destruction has been studied in any detail; information on the radiolysis of the other nucleotide bases is almost nonexistent). The strand breaks formed in irradiated DNA may contribute to a considerable extent to the loss of functional activity of DNA as measured *in vitro* by transcription with RNA polymerase or by the transforming activity of bacterial DNA. Attempts have been made to characterize the end groups formed by radiation-induced chain breakage using enzymes which react specifically with hydroxyl- or phosphate groups on the 3'- or 5'- end of the strand break. In DNA irradiated *in vitro* about 90% of the 5'-ends carry phosphate groups. Only 1/3 of the strand breaks in DNA of irradiated cells carry 5'-hydroxyl or 5'-phosphate groups. It is not known why 2/3 of the 5'-ends are unreactive in this test. A study of the end groups in the DNA of irradiated cells with terminal transferase showed that about 70% of the actual strand breaks carried 3'-hydroxyl end groups. In a study of the 3'- and 5'-end groups in the DNA of irradiated thymocytes in the course of a postirradiation period, there was a decrease of strand breaks in the first 15 min accompanied by a corresponding disappearance of 5'-phosphate and 3'-hydroxyl end groups. It is suggested that only those strand breaks were repaired that carried 5'-phosphate and 3'-hydroxyl end groups. (32 references)

- 6615 IMMUNOFLUORESCENCE STAINING OF DNA TUMOR VIRUS-INDUCED ANTIGENS. (Eng.) Tevethia, S. S. (Tufts Univ. Sch. of Medicine, Boston, Mass., 02111). *Ann. N.Y. Acad. Sci.* 254:541-550; 1975.

Of serologic tests available for detection of antigens in tumor cells, the indirect immunofluorescence test is the most powerful. Antigens present in cells transformed by papovaviruses, or in tumors induced by the viruses, can be classified into intracellular antigens and surface antigens. The intracellular antigens include tumor (T) and (U), present in

transformed cells and tumors; and virion (V) antigen, which appears 20-40 hr after infection of permissive monkey cells with SV40. All three antigens are located in the nucleus; the T antigen also appears in the cytoplasm and the U antigen can be perinuclear. The surface antigens include face (S) antigen, and embryonic antigens, but the TSTA can be distinguished only by tests that measure cellular immunity. The lack of a relationship between TSTA and S appears established. Viruses recently isolated from human cases of progressive multifocal leukoencephalopathy and from the urine of patients who had undergone renal transplantation show papovavirus morphologic features, grow in human cells, transform hamster cells, and induce tumors *in vivo*. The viruses induce T antigen that is antigenically similar to simian virus 40 (SV40) T antigen; the viral antigen of the viruses also cross reacts with SV40 viral antigen, demonstrable by the indirect immunofluorescence test. (50 references).

- 6616 ONCOGENIC PROPERTIES OF HUMAN VIRUSES.
(Eng.) Glaser, R. (The Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa. 17033); Decker, B.; Rapp, F. *In Vitro* 11(3): 151-165; 1975.

An overview of the status of DNA tumor viruses and their relation to human cancer and to transformation is presented. Human papovaviruses, human adenoviruses, and the herpesvirus group, including herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV), are discussed. Five new human papovaviruses recently have been isolated, three from brains of patients with progressive multifocal leukoencephalopathy, and two from the urine of immunosuppressed patients who had undergone renal transplants. Two of the viruses isolated from the brain appear to be related to simian virus 40. Research on papilloma viruses has been performed with Shope papilloma virus; the study of human papilloma virus has been limited because sources of the virus are difficult to obtain. The role of this virus in benign tumors and its association with the production of malignancy is still unknown. The authors state that "at present, there is little evidence that adenoviruses play a causative role in human cancer." Recently, most research has been concerned with the herpesvirus. It is responsible for some naturally natural host for a variety of herpesvirus, including herpes simplex type 1 (HSV-1) and HSV-2. HSV DNA and RNA has been identified in a cervical tumor, and it was demonstrated in exfoliated cells from cervical cancer patients. The demonstration of the transforming ability of both HSV-1 and HSV-2 transformation of mouse and hamster cells supports the possible connection between herpesvirus and human malignancy. Human CMV has also been examined for oncogenic potential. UV-irradiated CMV transformed exposed hamster embryo fibroblast cells; when the CMV-transformed cells were inoculated into newborn hamsters, tumors were induced. EBV has also been studied as the etiologic agent for Burkitt's lymphoma and nasopharyngeal carcinoma. Evidence supporting this theory is presented. No human C-type RNA virus has been identified, although it has been reported in other primates. Accumulating evidence favors a

role for viruses in the etiology of cancer, including that of man. Oncogenic transformation of cell cultures and the subsequent induction of transplantable tumors in animals can be associated with biological activity of at least some herpesviruses. (137 references)

- 6617 PROPERTIES OF CELLS TRANSFORMED BY DNA TUMOR VIRUSES. Butel, J. S. (Baylor Coll. of Medicine, Houston, Tex. 77025); Estes, M. K. *In Vitro* 11(3):142-150; 1975.

The process of cell transformation by simian virus 40 (SV40) and polyoma virus, and the properties of the transformed cells are discussed. Interactions of SV40 and polyoma virus with nonpermissive and permissive cells are summarized. Cell alterations induced by DNA in transformed cells may be morphologic, metabolic, or antigenic; alterations that can be used as markers of virus-transformed cells include the loss of contact inhibition and changes from fibroblastic to epithelioid cell shapes. Factors that affect the frequency of transformation are the genetic makeup of the host cell, the physiologic state of the cells, the multiplicity of infection, and the genetic composition of the virus. Virus markers useful in determining the etiology of virus-free tumors are virus-specific DNA, virus-specific messenger RNA, virus-induced antigens, and the rescue of infectious virus. The most frequently used markers are virus-induced antigens, including tumor antigen (located in the cell nucleus), and tumor-specific transplantation and surface antigens (both of which appear on the surface of transformed cells). The loss of contact inhibition and changes in morphology can be used as markers of virus-transformed cells, in addition to antigenic changes in the cell. The most important method of virus rescue involves transfection or DNA transfer, in which high-molecular wt DNA from transformed cells is passed into permissive cells in the presence of DEAE-dextran. Rescue of infectious virus indicates that the entire viral genome is present in at least some transformed cells. The use of temperature-sensitive mutants of SV40 and polyoma virus has shown that one or more viral genes are also involved in the initiation and maintenance of transformation. The accumulated data suggest that interactions between viral and cell functions may be required to maintain the transformed phenotype. (61 references)

- 6618 TUMOUR VIRUSES DISCUSSED AT COPENHAGEN.
(Eng.) Macpherson, I. (No affiliation given.) *Nature* 258(5530):17-18; 1975.

The nature of the C-type viruses apparently isolated from the bone marrow of a lymphosarcoma patient, from the leukocytes of an acute myeloid leukemia patient, and from cultured human embryo lung cells is discussed. While all three viruses are recognized as typical C-type particles, competition radioimmunoassay analysis and molecular hybridization have revealed that the latter two isolates each contain two distinct viruses with close affinities to simian sarcoma virus and baboon endogenous virus. Furthermore, the demonstration that most adult human sera contain antibodies that combine with polypep-

tides from these C-type RNA tumor viruses suggests their widespread occurrence in the human community. Human complement, without the intervention of antibodies, is capable of lysing a wide range of C-type viruses. A cDNA *onc* gene probe was made by absorbing radioactive DNA complementary to the RNA genome of an avian transforming virus, onto the RNA of a mutant (nontransforming) virus. Methylcholanthrene-induced tumor cells from quail contained RNA homologous to the probe, suggesting a link between chemical induction of tumors and the activation of "viral" genes. The lack of measurable homology of human genital and laryngeal warts with complementary RNA prepared from plantar wart DNA suggests the existence of a variety of papilloma viruses, some of which may be responsible for malignant tumors. (No references)

- 6619 TUMOR VIRUSES AT COLD SPRING HARBOR.
(Eng.) Gallo, R. C. (Natl. Cancer Inst., Bethesda, Md.); Levine, A. *Cell* 2(4):295-304; 1975.

Extensive reports are made on both DNA and RNA viruses. Progress in mapping and sequencing simian virus 40 (SV40) DNA include techniques employing temperature sensitive (ts) mutations, restriction enzymes, molecular hybridization, and heteroduplex mapping. A variety of cells transformed by SV40tsA showed differences in colony morphology, saturation density, growth in soft agar, and growth on monolayer cultures at the permissive *versus* the nonpermissive temperatures. SV40 mutants affect the maintenance of the transformed state in some undetermined way. Using restriction-enzyme fragments, the adenovirus genome were located, and different size polyosomes were assigned to transcripts from different fragments. Reports on Herpes simplex virus, primarily on Herpes DNA, include studies on the genome of and translational controls. Progress in characterization of Epstein-Barr Virus (EBV) DNA is slow, but reports include its association with Burkitt's lymphoma and its disputed role as a passenger virus. Seven general areas in the study of RNA viruses are emphasized. The major issues under study of endogenous type C viruses concern their origin, evolution, and origin of their tumor-inducing nucleotide sequences. There is evidence for recombinant viruses. The purification and characterization of viral structural proteins and enzymes and observations on the nature and the reproduction of the viral RNA genomes are reported. Studies of primate systems and the origin of type C viruses reveal the appearance of two types of apparently unrelated type C primate viruses; studies on human neoplasias were limited to leukemias and bear on the relationships between primate viruses. Presumably because of difficulties in pursuing the problem, relatively few reports were made on the precise nature of the phenotypic change leading to transformation; reports on the problem centered on the plasma membrane. Details of viral genome structures, polynucleotide sequence, the viral transcripts and proteins are all becoming better defined. Probes used in this definition are the various restriction enzymes, Cot analysis, electron microscopy, and RNA sequence analysis. Tumor viruses may be a probe for the study of mammalian cells in culture, just as bacteriophages have been for the study of bacteria. (No references)

- 6620 THE CONTROL OF CELL GROWTH REGULATION BY TUMOR-INDUCING VIRUSES: A CHALLENGING PROBLEM. (Eng.) Dulbecco, R. (Imp. Cancer Res. Fund Lab., London, England). *Proc. R. Soc. Lond. [Biol.]* 189(1094):1-14; 1975.

The control of cell growth by tumor-inducing viruses is discussed. Normal cells stop at a constant point in the growth cycle (G1 phase); this is in contrast to transformed cells, which stop or slow down at any phase. The main reason for decreased protein synthesis in resting cells (fibroblastic culture) is the alteration in ribosomes into free polysomal particles. Topoinhibition also exists in continuous cell layer cultures, and is not due solely to medium exhaustion. Calcium, although used at a very low rate, is a stimulatory factor in BALB/c3T3 cell growth. Other fibroblast growth factors include: serum, some large proteins, fibroblastic growth factor, cortisol, and insulin. Potentiators may also be required for inducing the formation of surface receptors for growth promoters. The variability of commitment times is the main variable factor of the growth cycle. The early events of growth induction include: phosphate and deoxyglucose transport and changes in cyclic nucleotide levels. Cyclic AMP levels are not important in this area, but cyclic guanosine monophosphate levels are affected by serum. Generally, the early changes are not necessary for the action of growth-promoting factors. Oncogenic viruses do not induce events equivalent to early events, but only induce intermediate and late events. Viral DNA replication begins later than host cell DNA formation, probably because both A protein (the protein specified by the viral gene A) and host cell mechanisms are required. A model for regulation of cellular DNA synthesis is presented, in which commitment to DNA replication requires condensation of unstable monomers of a regulator protein to form stable oligomers on the DNA of a regulator gene. Enhancement of the overall rate of protein synthesis may be a key step in growth activation. (46 references)

- 6621 NASOPHARYNGEAL CARCINOMA: EVIDENCE FOR VIRAL AND IMMUNOGENETIC FACTORS. (Eng.) de-Thé, G. (International Agency Res. Cancer, 150 cours Albert Thomas, 69008, Lyon, France); Simons, M. J. *Proc. Int. Cancer Congr. 11th. Vol. 6 (Tumors of Specific Sites)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 123-127.

Evidence supporting the association of herpesvirus (Epstein-Barr virus, EBV) and nasopharyngeal cancer (NPC) is presented. In addition, basic epidemiology and pathological characteristics and genetic factors associated with this tumor are reviewed. NPC is a frequent tumor among males in China, Southeast Asia, the Maghred countries, Sudan, and East Africa. Familial clustering demonstrated in Hong Kong indicated as association of genetic factors and NPC. The association of EBV and NPC is based on serologic and virologic evidence. NPC patients from high (China), medium (Tunisia, Kenya, Uganda), or low (Europe, America) risk groups regularly exhibit high serological reactivities to EBV (i.e.,

antibodies against structural antigens, early and membrane antigens, complement fixing soluble antigens, and nuclear antigens). The presence of EBV fingerprints in epithelial nasopharyngeal tumor cells also supports the association of this carcinoma and EBV and indicates that this virus is not strictly lymphotropic. Molecular virological techniques, involving DNA hybridization experiments demonstrated EBV genomes in NPC biopsies from various parts of the world. EBV-specific nuclear antigen can be detected in NPC biopsies directly or after passage in nude mice. *In vitro* transforming activity on human and other primate lymphocytes and *in vivo* oncogenic potential after inoculation of primates support the possible EBV oncogenic activity in man. Highly significant differences in HL-A type found between Chinese NPC patients and controls suggest a characteristic genetic profile for NPC patients. The HL-A antigen profile associated with high risk comprised an increased frequency of the first locus antigen and a deficit in the frequency of antigen detected at the second locus, suggesting that an additional antigen existed which was undetectable by the reagents used and that is responsible for the increased NPC risk. The serological results do not necessarily imply a causal relationship between NPC and EBV. Therefore, the authors suspect that the main NPC disease susceptibility gene locus is located near the second serologically detectable HL-A locus. NPC offers a unique situation through multidisciplinary and multinational studies for the understanding of viral and immunogenic factors in the development of nasopharyngeal carcinoma. (28 references)

- 6622 IMMUNOGENETIC ANALYSIS OF THE MECHANISM OF INDUCTION OF FRIEND VIRUS LEUKEMIA. (Eng.) Eckner, R. J. (Dept. Pathology, Boston Univ. Sch. Medicine, 80 East Concord St., Boston, Mass. 02118); Kumar, V.; Bennett, M. *Transplant. Proc.* 7(2):173-184; 1975.

The helper-dependent properties of Friend spleen focus-forming virus (SFFV), the presence of defective interfering particles, and recent findings concerning the cellular basis for the genetic resistance to Friend virus (FV)-induced leukemia are reviewed. Analysis of the defectiveness of Friend SFFV for focus formation *in vivo* has increased understanding of the relationship between SFFV and its associated murine leukemia-inducing helper virus. A schematic representation of the infectious cycle of Friend SFFV is summarized. The enhancement of Friend virus leukemia by mycoplasma and achleplasma extracts that has been shown in BALB/c mice is discussed. The discovery of defective interfering particles in stocks of many different types of viruses and the successful use of an infectivity assay and complex dose-response analyses are also described. Numerous studies of the cellular basis for genetic resistance to erythroleukemia induced by FV are cited. Experiments on the role of target cells are consistent with the notion that both Fv-1 and Fv-2 also control properties of hemopoietic target cells. Studies of the role of cells mediating marrow allograft rejection (M cells) support the concept that M cells contribute greatly to the genetic resistance to FV complex. It has been

postulated that resistance genes other than Fv-2 affect the properties of M cells that are present in thymus-cell and spleen-cell suspensions. Studies on the role of cells mediating humoral immunity have indicated that resistance genes apparently do not control inherent properties of B cells themselves. The reported evidence thus suggests that genes other than Fv-1 and Fv-2 control properties of M cells that affect the susceptibility of mice to FV-induced leukemia. (51 references)

- 6623 THE FOAMY VIRUSES. (Eng.) Hooks, J. J. (Natl. Inst. Dental Res., Bethesda, Md. 20014); Gibbs, C. J., Jr. *Bacteriol. Rev.* 39(3):169-185; 1975.

Studies on simian foamy viruses (SFVs) are reviewed, and the limited literature on other foamy viruses is also reviewed. The foamy virus group of syncytium-forming viruses are all RNA viruses; they all have a reverse transcriptase; and they are morphologically similar. Early reports of the cytopathic effect and the isolation of SFV type I, SFV type II, bovine syncytial virus, hamster foamy virus, and of feline syncytium-forming virus are discussed. While agreement on the classification of foamy viruses has not yet been achieved, it is suggested that the foamy viruses from monkeys, apes, cows, cats, hamsters, and possibly man be incorporated as an independent group of viruses or as a subgroup of the leukoviruses. The isolation of these viruses from various primate species, the discovery of eight serotypes, and the lack of serological cross-reactivity and lack of foamy virus subgroup antigens are described. Morphological studies have revealed spherical viruses, ring-shaped intracellular particles, and spikes; however, detailed knowledge of their chemical structure is not yet available. Sensitivity of the SFV to physical and chemical agents is described, and the cultivation of SFVs in a variety of mammalian cell lines is noted. The time of the appearance of the cytopathic effect *in vitro* varies with serotype of the virus, the virus titer, the passage history, and the type of cells used to propagate the virus; two plaque assay systems are described and a typical growth curve is presented. Studies of virus replication have shown virus attachment and entry *via* direct entry or viropexis, characteristic nuclear fluorescence, the location of virus internal components within the chromosome structure, and viral maturation *via* budding from the cell membrane. Three routes of foamy virus spread are described; and a comparison of the properties of foamy viruses and leukoviruses is presented. Virus distribution in natural and experimental hosts is described, and horizontal and natural viral spread are noted. Sero-epidemiologic studies have revealed the widespread but species-specific distribution of antibody to the foamy viruses within the natural host population, and factors possibly influencing the persistence of such viral infections are discussed. However, the exact role of defective interfering particles, temperature-sensitive mutants, and/or defective cell-mediated immunity remains to be determined. (78 references)

- 6624 25th ANNUAL MEETING TISSUE CULTURE ASSOCIATION, INC. INTRODUCTORY REMARKS TO FOR-MAL SYMPOSIUM: CARCINOGENESIS *IN VITRO*. (Eng.) DiPaolo, J. A. (No affiliation given). *In Vitro* 11(2):87-88; 1975.

A historical review of *in vitro* models and an evaluation of the relevancy of tissue culture techniques for the study of cancer are presented. Numerous early reports that cancer of normal cells in tissue culture was produced directly by carcinogenic agents later appeared to be the result of accidental infection of the cultures with Rous virus. Experimental evidence exists that cellular hereditary factors are the most important determinant of tumor initiation. Lung grafts from A-mice produced more tumors in recipient A-mice when the grafts were "insulted" at fetal, rather than older ages. In this case the potential for neoplastic change depended on specific cellular factors; the genetic background was constant. Many studies have shown the transformation of cells in culture by chemicals; these cells producing malignant tumors in animals. One of the most striking developments is the acceptance of the concept that cancer cells are recognized as foreign by the host, and that the immune defense reactions are thus provoked. The studies selected for the symposium are those using a broad range of cells and agents in carcinogenesis. (No references)

- 6625 BASOPHILIC LEUCOCYTES: STRUCTURE, FUNCTION AND ROLE IN DISEASE. (Eng.) Dvorak, H. F. (No affiliation given); Dvorak, A. M. *Clin. Haematol.* 4(3):651-683; 1975.

Current knowledge of basophil structure, function, and role in disease, and conclusions derived from human studies and animal experiments are reviewed. Physiological and pathological variations in basophil frequency and distribution, as altered by adrenal, thyroid, and sex hormones, are described. Morphology of mature human basophils has been studied by phase-contrast and electron microscopy. Differences existing in the ultrastructural appearance of basophil granules in various species are noted, as are ultrastructural studies of basophil differentiation. Preliminary studies of the biochemical contents of basophils center on histamine synthesizing capacity, acid mucopolysaccharide content, and platelet activating factor. While the proteins of basophil granules remain poorly characterized, a variety of oxidative enzymes are identified. The interaction between immunoglobulin E (IgE) and the basophil surface is discussed, and several mechanisms of IgE-mediated histamine release are proposed. The expression of cutaneous basophil hypersensitivity is discussed. An animal's capacity to mount basophil-rich, delayed onset skin reactions is inversely related to the presence of basophils coated with specific antibody. In addition, data on the role of basophils in cell-mediated reactions in man are presented. Studies of basophil chemotaxis suggest mechanisms by which basophils may be attracted to delayed-type skin reactions and to inflammatory sites in general. The capacities of basophils for phagocytosis and pinocytosis are reported, and IgE-mediated anaphylactic basophil

degranulation is described. A new general model of basophil degranulation, capable of accounting for the varied rates of granular substance release occurring under various physiological and pathological circumstances, is presented. (125 references)

- 6626 TUMOR IMMUNOLOGY. (Eng.) Mitchell, M. S. (Yale Univ. Sch. Medicine, New Haven, Conn.). *Conn. Med.* 39(9):536-539; 1975.

Some of the principles of tumor immunology and tumor immunotherapy are described. The evolution of the concept of tumor antigenicity is discussed, and early preimmunization experiments illustrating the uniqueness of tumor antigens are cited. Specific demonstrations of neoantigens on tumors with immunofluorescence techniques and *in vitro* cytotoxicity tests have been recently reported. In virus induced tumors, there are antigens common to all tumors that are characteristic of the particular virus regardless of the strain or species of the host. In contrast, tumors induced by carcinogens have unique antigens. The immunosuppressive action of many carcinogens may allow the expression of a latent virus. The particular antigens that are expressed may not be neoantigens, but rather embryonic antigens; "carcino-fetal" substances so described include the carcino-embryonic antigen common to all adenocarcinomas of the gastrointestinal tract and the more specific appearance of alpha-fetoprotein. The lack of tumor rejection is discussed; permanent or temporary host immunological incompetence, lack of antigenic recognition, and lack of immune rejection capacity are all considered. The concept of immunological surveillance has been proposed, and the involvement of a thymus-derived small lymphocyte (T-cell) in the surveillance has also been suggested. A discussion of examples of the breakdown of surveillance includes the Wiskott-Aldrich syndrome, ataxia telangiectasia, and the experiences of renal transplant recipients. Other suggestions of immuno-incompetence predisposing to tumors include the functionally deficient T-lymphocytes of Hodgkin's disease and the lowered immunocompetence of the aged. The possibilities of the existence of immunological tolerance, serum "blocking" factors, and the "enhancement" phenomenon are also discussed. Cytotoxic antibodies capable of killing tumor cells in the presence of complement *in vitro* are reported. A macrophage-mediated immunity involving the product of a non-thymus dependent lymphocyte (B-cell) is also suggested. A diagram schematizing the interaction of the three principal cells involved in tumor destruction is presented. Some studies have indicated that some chemotherapeutic agents and schedules of chemotherapy may not be antagonistic toward the host's defenses despite their potential for immunosuppression. (3 references)

- 6627 NEOANTIGENS ON CARCINOGEN INDUCED TUMOURS. (Eng.) Bladwin, R. W. (Cancer Res. Campaign Lab., Univ. Nottingham, England). *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 222-227.

The expression of neoantigens on carcinogen-induced

tumors and the immune responses in the tumor-bearing host are reviewed. Neoantigens expressed by cells transformed by chemical carcinogens demonstrate a high degree of specificity; however, a high degree of variability in immunogenicity exists between tumors of comparable histological type but induced by different chemicals. Tumor-associated cell surface antigens are characterized on many chemically-induced tumors by *in vitro* tests of cell-mediated and humoral immune reactions in tumor immune or tumor bearing hosts. While induced or spontaneous mammary carcinomas generally lack demonstrable immunogenicity, tumor-directed cell-mediated immune responses can be demonstrated in rats bearing these tumors by the *in vitro* cytotoxicity of lymph node cells. Tumor type-specific neoantigens are also identified by *in vitro* lymphocytotoxicity tests on carcinogen-induced murine bladder carcinomas and rat colon carcinomas. In addition to the organ specific embryonic antigens, rat mammary carcinomas, colon carcinomas, and others express cross-reacting embryonic antigens. Results of immunization studies on syngeneic rat hepatomas and sarcomas have suggested that the tumor injection response may be dependent upon the ability of the target cell antigen to function as an appropriate receptor for sensitized lymphoid cells or antibody which mediate reactions leading to tumor cell killing. In comparison, the tumor-associated embryonic antigens on hepatoma D23 cells is located both at the cell surface and in the intracytoplasmic fraction; this finding suggests its continuous synthesis in the cytoplasm. *In vitro* assays note that lymphoid cells from tumor-bearing, tumor-resected, and actively immunized individuals show similar cytotoxicities for the appropriate target tumor. Such abrogation of cell mediated cytotoxicity is subdivided into blocking reactions and direct inhibition. Blocking reactions with sera of tumor-bearing hosts are demonstrated in a wide range of studies; inhibition of cell-mediated toxicity *in vitro* following interaction of tumor-bearer serum is also shown in numerous tumor systems. The type and degree of interference with cell-mediated immunity by circulating serum factors during tumor growth is dependent upon the characteristics of the tumor and the immunocompetence of the host. It is evident that not all tumors will produce a consistent pattern of response; some tumor-associated antigens are released into the circulation more readily than others. There is substantial evidence that tumor antigen-containing moieties are implicated in the failure of a host to develop immunity toward a developing tumor. (53 references)

- 6628 QUANTITATION AND CHARACTERIZATION OF EFFECTOR CELLS AND THEIR PROGENITORS. (Eng.) Phillips, R. A. (Inst. Medical Science, Univ. Toronto, Toronto, Canada); Clark, D. A.; Schilling, R. M.; Miller, R. G. *Proc. Int. Cancer Congr. 11th. Vol. 1 (Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1975. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 264-269.

The derivation of a mathematical expression relating the degree of cytotoxicity to the number of

cells tested is presented, and subsequent studies on the characterization of effector cells and cell interactions involved at various stages in the development of the cell-mediated immune response are described. A model system on the lysis of P815 mastocytoma cells by allogeneic cells previously sensitized to alloantigens is described and employed in the quantitative assays. The basis of the quantitative assay is a reproducible and predictable relationship between target cell destruction, i.e. percent release of ^{51}Cr from labeled target cells (%Cr) and the number of lymphoid cells tested; plots of %Cr vs numbers of killer cells tested generally yield a series of parallel lines. The observations on which the mathematical is based note that killing is specific, that destruction of the target occurs by direct contact between the killer cell and the target, and that a single killer cell can destroy many target cells. An expression relating the number of viable, undamaged target cells at a time after mixing to the number of target cells mixed with a fixed number of lymphoid cells containing an unknown number of killer cells is derived. The mathematical model predicts that at a constant time, %Cr should be a linear function of the number of lymphoid cells assayed; this prediction has been confirmed experimentally. The model also predicts that at a constant number of lymphoid cells, %Cr should be a linear function of the incubation time, t . However experiments showed that %Cr varied with t^2 and not t . This contradiction of the model has been shown to result from the fact that ^{51}Cr release from a damaged cell is a time-dependent process. Incubation of the cells at 45 C for 1 hr at the end of the incubation at 37 C incubation overcomes this problem. However, more recent studies with mixed leukocyte culture cells show little deviation from the predicted values. Evidence that immunized mice contain cells that inhibit various *in vitro* assays for cell-mediated immunity is presented. Studies on the progenitors of killer lymphocytes focus on the *in vitro* response of one tissue, spleen, and attempt to isolate functionally different and separately inactive cell populations by cell separation techniques. The results indicate that two types of cells are required during the initiation of a culture to generate killer cells. Thus, while the mathematical model gives only relative measures of activity, other studies indicate the presence of cells capable of inhibiting the cytotoxic reaction and suggest an interaction of at least two different types of cells prior to the initiation of a cell-mediated response. (17 references)

- 6629 LYMPHOCYTE SURFACE IMMUNOGLOBULINS. MOLECULAR PROPERTIES AND FUNCTION AS RECEPTORS FOR ANTIGEN ARE DISCUSSED. (Eng.) Marchalonis, J. J. (Walter Eliza Hall Inst. Medical Res., P.O., Royal Melbourne Hosp., Victoria 3050, Australia). *Science* 190(4209):20-29; 1975.

The possible recognition role of the membrane-associated immunoglobulin related to immune macroglobulin antibodies (i.e., the immunoglobulin M, [IgM], class) in many immunologically specific reactions of both B (bone marrow-derived) and T lymphocytes (thymus-derived) is discussed. Immunoglobulins

have been isolated from the surface of B and T lymphocytes. Two types of membrane immunoglobulin occur on B lymphocytes. One type resembles the 200,000-dalton subunit of IgM and the second possesses a heavy chain electrophoretically distinct from μ chain that does not correspond to any of the known classes of mouse immunoglobulins. The authors suggest that it might correspond to human δ chain. T lymphocytes possess only one type of surface immunoglobulin. This molecule has a mass of approximately 200,000 daltons and contains light chains and heavy chains similar to but not identical to μ chains. Evidence now exists that surface IgM-like lymphocytes activated to certain antigens can bind specifically to antigen. These observations suggest that surface immunoglobulin functions as a receptor for antigen on B cells and at least on some T cells. The mechanisms by which combination of antigen with surface immunoglobulin initiate differentiation remain to be determined. (106 references)

6630 ANALOGIES BETWEEN EMBRYONIC (T/t) ANTIGENS AND ADULT MAJOR HISTOCOMPATIBILITY (H-2) ANTIGENS. (Eng.) Artzt, K. (Cornell Univ. Medical Coll., New York, N.Y. 10021); Bennett, D. *Nature* 256(5518):545-547; 1975.

Analogies between mouse embryonic (T/t) antigens and the adult major histocompatibility complex (MHC, H-2 antigens) are presented. The T/t complex and the H-2 complex are linked on chromosome 17 with T/t 14 crossover units to the left of H-2. In the presence of most lethal and sublethal t alleles, recombination between t and H-2 is suppressed, suggesting that the two loci act as a functional unit for maintaining heterozygosity at H-2 in feral populations of mice. Secondly, each complex occupies a large region of the chromosome; H-2 complex spans 0.4 cmorgans, but the T complex has not yet been measured. In addition, both T/t and H-2 specify complex and highly polymorphic codominant antigens on the cell surface; each H-2 haplotype of independent origin encodes on the average eight specificities and t haplotype mutants have three of four specificities. Fourthly, each complex has a minimum of two serologically detectable genes and fifthly, the developmental expression of H-2 and T/t antigens seems to be reciprocal. H-2 is present on all adult cells except sperm cells, but absent from the early embryo. On the other hand, T/t is absent from all adult cells except germ cells, but is present on embryonic cells. Sixth, both systems seem to have analogues in other species (e.g., mammals and birds) and finally, recent biochemical evidence suggests that the antigenic products of both T/t and H-2 are structurally similar. These considerations suggest that the T/t complex may be an evolutionary precursor of the MHC, or that both complexes originated in a common ancestral gene. (34 references)

6631 PRIMARY ANGIOSARCOMA OF THE LIVER: REVIEW ARTICLE. (Eng.) Alrenga, D. P. (Cook Cty. Hosp., Chicago, Ill.). *Int. Surg.* 60(4): 198-203; 1975.

Characteristics of primary hepatic angiosarcoma and

infantile hemangioendothelioma are reviewed. Angiosarcoma forms 1.8% of all primary liver cancers, with an autopsy incidence of six per 100,000 and no geographic variation. The best known causative agent is ThO₂ (Thorotrast); there is an average latent period of 22 yr, with 70% of the injected material heterogeneously accumulating in Kupffer cells of the liver. Hepatic angiosarcoma is also attributed to gamma radiation, As₂O₃, and vinyl chloride exposure. Infantile hemangioendothelioma is analogous to hepatoblastoma and mesenchymal hamartoma. Clinical features of angiosarcoma included 85% of the cases occurring after age 40, with males predominating over females 2:1 and an extremely variable mode of presentation. The most common symptoms include rapid hepatic enlargement, epigastric pain, ascites, and jaundice. Seventy percent of hemangioendotheliomas were diagnosed prior to 6 months of age; males predominate 2:1. Abdominal distension, vomiting, diarrhea, or constipation are the most frequent symptoms. The gross morphology of both forms is similar; this includes solitary, multicentric, or diffuse tumors, varying from solid fleshy nodular masses to large blood-filled cystic spaces. Four types are described: diffuse hemangioendothelioma, angioplastic reticulosarcoma, hemorrhagic reticulosarcoma, and solid reticulosarcoma. Angiosarcoma differs from infantile hemangioendothelioma. Other infantile hemangioendothelioma-associated conditions include polycystic kidneys, hydatid cyst, Klinefelter's syndrome, and a significant number of cutaneous hemangiomas. Angiosarcoma has an unfavorable prognosis; most cases run rapid and fulminant courses with patients dying of hepatic failure or generalized metastases. Infantile hemangioendothelioma has a more favorable prognosis. Partial hepatectomy, radiation, steroids, and hepatic artery ligation give successful results; there is also some suggestion of spontaneous involution and regression. (50 references)

6632 ZOLLINGER-ELLISON SYNDROME: A REVIEW. (Eng.) Gerstein, J. D. (Walter Reed Army Med. Cent., Washington, D. C.); Muir, R. W. *Am. Surg.* 41(4):230-239; 1975.

The major clinical, diagnostic, and therapeutic aspects of the Zollinger-Ellison syndrome (ZES) are presented. Gastrin, a 17-amino acid polypeptide, is a stimulator of acid production in both the cephalic and gastric phases of digestion, with acetylcholine release as the final pathway in gastrin-stimulated acid liberation. A number of theories are evolved for the etiology of the ZES and the more inclusive syndrome of multiple endocrine adenomatosis. In addition to the supposition that the endocrine-secreting cells of foregut origin develop from precursor cells in the neuroectodermal neural crest and subsequently migrate, an underlying autosomal dominant genetic defect is also assumed to be involved in the pathogenesis of ZES. A second genetically-based theory postulates a primary islet cell defect with resulting proliferation of the primordial islet cells. An undetermined "gastric factor" is hypothesized to play a major role in the pathogenesis of the ZES. The pituitary-hypothalamic axis is also implicated. Clinically, the essential

features of ZES include duodeno-jejunal or recurrent stomach ulceration, gastric hypersecretion and non-beta islet cell tumors of the pancreas. Initial symptoms most frequently presented include pain, fluid loss, and bleeding. A study of multiple endocrine adenomatoses revealed a familial association of adenomas arising in the pituitary, parathyroids, and pancreatic islets. The definitive test for diagnosis of the ZES in a patient with ulcer disease is the serum gastrin level; indirect and direct techniques are described. Management of the disease includes endocrinological screening, serum calcium and phosphate determinations, plus pituitary and thyroid evaluations. Medical measures generally only delay the needed operation; total gastrectomy with removal of the end organ consistently yield the best results. Long-term follow-up and evaluation of the patient and his relatives are required because of the familial, (multi-) glandular, and polyhormonal nature of the disease. (58 references)

- 6633 ORIGIN OF PREMALIGNANT LESIONS OF CERVIX UTERI. (Eng.) Coppleston, M. (No affiliation given); Reid, B. *Prog. Gynecol.* 6:517-539; 1975.

Following a brief discussion of present popular trends and concepts of the pathology, epidemiology, and possible etiological agents, studies of the transformation zone of the human cervix uteri are reviewed. Clinicopathological studies of squamous cancer note the early manifestations, sequences of alterations, and question the origin of the various preneoplastic epithelia. Epidemiological studies reveal several secondary factors and two significant recurring variables: early onset of coitus and a history of multiple sexual partners. Suspicion and studies largely center on biological agents introduced during coitus; herpes virus is especially suspect, as is the sperm head itself. Local studies, aimed at discovering stages prior to the appearance of obvious histological abnormalities, examine the process initiating the tissue at risk, dynamic phases of epithelial activity, predisposing properties of neoplastic change, possible etiological agents, and the mechanism of initiation of carcinoma. Combined colposcopic-histological-experimental studies of the biology of the transformation zone are described and illustrated in depth. A hypothesis, implicating metaplasia as the key process in the development of squamous cancer of the cervix is presented. Microscopic autoradiography, histochemical, and biochemical techniques reveal the uptake of gamete DNA by certain cells of the female genital tract, and the condensation of DNA by histones. The authors postulate that the release of basic proteins during postcoital degradation of sperm on the cervix may encourage production of surface DNA by differentiating cells. If these cells are undergoing metaplasia, their surface DNA may be motile. A "potentially carcinogenic mechanism," discussed elsewhere by the authors, may be initiated. (37 references)

- 6634 ELECTRON MICROSCOPY OF PITUITARY TUMORS. (Eng.) Racadot, J. (Dept. Histology and Embryology, Faculty of Medicine, Pitié-Salpêtrière,

105 boulevard de l'Hôpital, 75634 Paris Cedex 13, France); Vila-Porcile, E.; Olivier, L.; Peillon, F. *Prog. Neurol. Surg.* 6:95-141; 1975.

Studies of the ultrastructure of adenomas of the anterior hypophysis are reviewed. Numerous electron micrographs are included. The cellular composition of the adenomas of the hypophysis is compared to the normal hypophysis, based on the light microscopic study of 300 adenomas. A summary of the generally accepted classification of the functional activity of the different cell types (i.e., "acidophilic" cells, "basophilic" cells, and "chromophobic" cells) is presented. The materials and fixation technique employed in the ultrastructural study of 46 adenomas are described. Morphological characteristics of these adenomas are correlated with the clinical data; findings concerned with the secretory granules, the cytoplasmic organelles, the abnormalities of the cytoplasm and the nucleus, and the relation of the cells to the connective tissue and blood vessels are tabulated and summarized. A study of adenomas obtained from 17 patients with acromegaly has demonstrated the presence of: two types of secretory granules, the absence of basal lamina, large and irregular nuclei, and hypertrophied nucleoli. The most striking cellular abnormalities, seen most frequently in adenomas containing few somatotrophic granules, are the development of spheroid bodies and mitochondrial abnormalities. An examination of 13 adenomas without evident hyperpituitarism (classical "chromophobe" adenomas) has revealed that they have a very variable architecture; submicroscopic granules and mitochondrial abnormalities were frequently noted, while abnormalities in other cellular organelles were variable and without any systematic distribution. Ultrastructural analysis of seven adenomas with menorrhagia-galactorrhea or hypogonadism-gynecomastia syndrome has also demonstrated the presence of variable-sized granules, nucleolar hypertrophy, and nonspecific anomalies of the organelles. Studies of the adenomas of ten patients with Cushing's disease have also shown secretory granules of several sizes, plus numerous intracellular filaments, lysosomes, and other nuclear or mitochondrial abnormalities. The electron microscopic observations from these cases are compared to other data in the literature. There is concordance of structural criteria with the clinical diagnosis in cases of hyperpituitarism, but discrepancies between morphological features and clinical diagnosis do occur. The observation of mitoses constitutes an important index of the proliferative capacity of an adenoma. Structural abnormalities in the cells (spheroid bodies, abnormal nuclei, nucleoli or mitochondria) are probably of more significance when they occur simultaneously. (41 references)

- 6635 A NEW ROLE FOR THE GLIAL CELL? (Eng.) Levi-Montalcini, R. (No affiliation given). *Nature* 253(5494):687; 1975.

Data which do not support a previously suggested new role for the glial cell are discussed. The suggested new role for the glial cell is based on a reported isolation from rat gliomas of a protein similar to NGF (nerve growth factor from mouse

salivary gland). However, these tumors were probably contaminated with fibroblasts, which could have been the source of NGF. Release of NGF by some fibroblastic cell lines has been reported. More convincing evidence for release of NGF by unequivocally identified glial cells should be obtained before NGF secretion by glial cells is accepted. (8 references)

- 6636 ERYTHROPOIETIN PRODUCTION IN RENAL TUMORS. (Eng.) Kazal, L. A. (Cardeza Found. Hematol. Res., Philadelphia, Pa.); Erslev, A. J. *Ann. Clin. Lab. Sci.* 5(2):98-109; 1975.

A review of the relation of erythropoietin production to the presence of renal neoplasm suggests that erythropoietin may be produced either directly by the tumor or indirectly by its physical effect on the adjoining renal tissue. As erythropoietin cannot be measured by any chemical parameter, its concentration in plasma and tumor tissue is best determined by bioassay, depending upon suppression of erythropoiesis in a rat or mouse. More recently, several *in vitro* assays were also employed, including tissue culture assays and immunologic assays. The incidence of erythrocytosis in the general population remains unknown but is regarded as exceedingly small. It is also found more frequently in patients with hydronephrosis and renal cysts than in those with renal tumors. The presence of erythropoietin in serum and/or tumor extracts of patients with hypernephroma and erythrocytosis appears to be a consistent finding; also, the effect of excision of hypernephromatous tissue is generally to reduce serum erythropoietin levels to control or near control levels, except in the case of occasional metastatic tumors. In the neoplastic renal tissue of some patients with erythrocytosis, analysis of extracts of hypernephromatous tumors demonstrated the presence of an erythropoietic activity, as expressed as percent ^{59}Fe utilization obtained by the hypertransfused, hypoxic, or starved rodent assays. The concentration of erythropoietin in some tumors suggests the existence of inappropriate neoplastic production of erythropoietin. However, the variety of tumors involved in erythropoietin production, its presence in only certain tumor extracts, and its discovery in nonneoplastic kidney disease suggest other than a neoplastic production of erythropoietin. Two hypotheses are advanced to explain erythropoietin production by renal tumors. One suggests that erythropoietin is synthesized by the renal tumor tissue. The other implies that pressure of the tumor on the normal portion of the kidney induces ischemia and local hypoxia, resulting in stimulated erythropoietin production in the remaining part of the kidney. (64 references)

- 6637 LEUKAEMIA CYTOGENETICS. (Eng.) Woodliff, H. J. (Cancer Council Western Australia, 220 St. George's Terrace, Perth, W. A. 6000, Australia). *Med. J. Aust.* 1(16):495-499; 1975.

Leukemia cytogenetics, the study of the chromosomes of cells from patients with leukemia, is reviewed in the following areas: acute leukemia, chronic

granulocytic leukemia, chronic lymphocytic leukemia, polycythemia vera, myelofibrosis and megakaryocytic myelosis. Many chromosome abnormalities have been described in numerous cases of acute leukemia, but no constant or typical chromosomal abnormality characteristic of the disease has been found. Chromosomal abnormalities seen in this form of the disease include: numerical changes, such as aneuploidy, polyploidy, endoreduplication and haploidy, and structural aberrations, such as deletions, marker chromosomes, pseudodiploidy, dicentric chromosomes, chromatid lesions and breaks, acentric fragments and an increase in secondary constrictions. A characteristic minute chromosome, called the Philadelphia chromosome (Ph^1), has been identified in chronic granulocytic leukemia. It is a small, acrocentric chromosome which has lost about half the substance of its long arms. It belongs to the G group and is considered to be one of pair 22 (some researchers assign it to pair 21). Of 52 patients examined in one study, 37 had bone marrow examinations and 41 peripheral blood examinations. Ph^1 -positive cells were found in all 52 patients. Most patients with polycythemia vera have normal karyotypes. Abnormalities which have been found are usually non-specific and no characteristic chromosomal lesion has been described. Some increase in random aneuploidy has often been seen in patients with myelofibrosis, but usually the karyotype is otherwise normal. In one study, 3/4 patients with megakaryocytic myelosis had normal karyotypes and one had Ph^1 -positive cells. In another study, 6/8 patients had a G 21 chromosome with elongated short arms. Most analyses, however, have shown only a normal karyotype. Apart from some increase in aneuploidy and the suggestion by some workers that pseudodiploidy may occur, cytogenetic studies in chronic lymphocytic leukemia have not uncovered any typical chromosome aberrations. It is concluded that the abnormalities, except for the Ph^1 chromosome, seen in leukemia patients, are likely to be secondary phenomena and not associated with the primary leukemogenic stimulus. The constancy of the Ph^1 suggests that it may be involved at least with pathogenesis if not with the etiology of chronic granulocytic leukemia. (31 references)

- 6638 THE CELL SURFACE. (Eng.) Berlin, R. D. (Univ. Connecticut Health Cent., Farmington); Oliver, J. M.; Ukena, T. E.; Yin, H. H. *N. Engl. J. Med.* 292(10):515-520; 1975.

Experimental evidence from studies of cell surface topography using cultured fibroblasts, lymphocytes, and phagocytic cells that demonstrated characteristic nonrandom distribution patterns for several different membrane components is reviewed. A proposal is made that structures extrinsic to the membrane, (e.g. microtubules) are important in determining its properties. It is postulated that for the membrane to exist in a state of lowest free energy, lipids and proteins must be arranged so as to maximize hydrophobic bond formation with the lipid, and hydrophilic groups interact with the aqueous environment; this model is designated the "fluid mosaic model". It allows considerable compositional differences between membranes, the accommodation of proteins thought to extend through

the membrane, and the prediction of no long-range forces intrinsic to the membranes. Experiments on membranes illustrate the existence of a random distribution of proteins free to move over the surface (homogeneous topography), plus a nonrandom distribution (heterogeneous topography). Topographic changes induced in cancer cells imply the existence of forces limiting free diffusion of membrane proteins, and suggest differences in the nature or effectiveness of restraining or limiting factors. Data on lectin binding to the cell surface confirm that ligand-receptor complexes are mobile on cell surfaces, and indicate that forces other than free diffusion are probably involved in the ordering of surface topography, including agents acting directly on the membrane and those affecting intracellular processes. Studies of lectin receptors on the plasma membrane of polymorphonuclear WBC indicate that some randomly distributed elements may become nonrandom during phagocytosis. A similar segregation of membrane proteins may occur during extrusion of nuclei from maturing reticulocytes. Evidence presented in support of surface topography regulated by the interaction of the plasma membrane with a specific class of cellular constituents resembling microtubular proteins suggests that microtubular proteins are essential for the heterogeneous topography induced by phagocytosis. Pharmacologic evidence implicates only a microtubular protein, and not necessarily the morphologically recognizable microtubule. However, it is proposed that a reversible association of microtubules, and perhaps microfilaments, with membrane components is induced by ligand or particle contact, and is involved in the movement of surface proteins. (16 references)

6639 NUCLEIC ACIDS IN THE PATHOGENESIS OF HUMAN LEUKEMIA. INTRODUCTORY REMARKS. (Eng.)

Polli, E. E. (Istituto di Clinica Medica I, Università di Milano, Via Francesco Sforza 25, I-20122 Milano, Italy). *Acta Haematol. (Basel)* 54(4):197-200; 1975.

Experimental evidence supporting the hypothesis of leukemogenesis by both DNA and RNA viruses is reviewed together with the results of physicochemical studies on RNA and DNA isolated from normal and leukemic cells. The latter studies have shown an accumulation of double-stranded RNA in the nucleus of leukemic lymphocytes. The author states: "Of interest seems to be the discovery of a high percentage of repeated sequences (poly A) in messenger RNA of leukemic cells, an unusual condition of nuclear RNA; and most impressive are the findings showing an accumulation of double-stranded RNA in the nucleus of leukemic lymphocytes." Normal and leukemic DNA contain families of nucleotide sequences with different repetitive frequencies. The most highly repeated sequences are satellite DNAs, and it is hypothesized that these may be related to the organization of chromosomes and cell replication. Other repeated nucleotide sequences with lower reassociation velocity than the very fast-renaturing satellite DNA have also been isolated. The possibility of viral information being integrated in these repeated sequences is noted. (7 references)

6640 HORMONE RECEPTORS IN HUMAN BREAST CANCER.

(Eng.) McGuire, W. L. (Univ. Texas Health Science Center, San Antonio, Tex. 78284). *Proc. Int. Cancer Congr. 11th. Vol. 5 (Surgery, Radiotherapy and Chemotherapy of Cancer)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 366-372.

The use of estrogen receptor assays to predict the results of endocrine therapy for metastatic breast cancer is reviewed. Two methods have been used to quantitate estrogen receptors in human breast cancer specimens. The first method makes use of the high affinity binding of [³H]estradiol, evaluated by equilibrating cytosol with various low concentrations of labeled hormone and then removing the unbound hormone with dextran coated charcoal; Scatchard plots of the binding data permit direct extrapolation to determine the amount of this component. The second method involves sucrose density gradient centrifugation in which the receptor primarily sediments at 8 S. Data on the correlation between clinical response to endocrine therapy and estrogen receptors are reported for 436 treatment trials in 380 patients. Thirty-three percent of 211 treatment trials of ablative therapy (adrenalectomy, castration, hypophysectomy) yielded objective tumor regressions. Eight of ninety-four trials (8%) in patients with negative tumor estrogen receptor values were successful; 59 of 107 trials (55%) in patients with positive values succeeded. Patients with borderline tumor estrogen receptor values had a 30% response rate. Thirty-four percent of 170 trials using additive therapy (androgen, estrogen, glucocorticoid) yielded tumor regressions. Seven of eight-two (8%) trials with negative values were successful; 51 of 85 (60%) trials in patients with positive values succeeded. Twenty-seven percent of 55 trials yielded responses to a variety of endocrine therapies including antiestrogens, aminoglutethimide, etc. Of 32 trials in patients with negative tumor estrogen receptor values 5 (16%) were successful, whereas 10 of 23 (43%) trials in patients with positive values succeeded. It is concluded that estrogen receptor assays can be helpful in predicting the results of endocrine therapy for metastatic breast cancer. (16 references)

6641 ENDOGENOUS HORMONAL CHANGES AS ONLY AND SUFFICIENT FACTORS IN THE ETIOLOGY AND GROWTH OF MAMMARY CANCER IN THE AxC RAT. (Eng.)

Iglesias, R. (Estado 57, Dep. 706, Santiago 1, Chile). *Proc. Int. Cancer Congr. 11th. Vol. 6 (Tumors of Specific Sites)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 8-13.

Three models of mammary cancer developed in the AxC mouse and excluding exogenous factors are discussed. They are tumors developed in rats grafted with: 1) spontaneous functional testicular tumors which produce androgens and estrogens; 2) spontaneous functional pituitary tumors which apparently produce prolactin only; and 3) functional

ovarian tumors. In four groups of eight animals each, of intact and castrated male and female AxC rats grafted with the testicular tumor, the frequency of pituitary tumors was 43.7% and of mammary tumors 46.8% (normal 6.9% and 1.8% respectively). The mammary tumors appeared 10-12 mo after inoculation of the testicular tumor and are deemed to be the result of the action of the estrogen produced by the grafted testicular tumor. The carcinogenic factor would be prolactin. In 16 animals inoculated with the third transplant generation of a pituitary tumor, mammary tumors developed in two intact females and in one spayed animal. Another pituitary tumor grew in six intact females that were inoculated; mammary tumors developed in two of the animals. One mammary tumor was grafted and grew in spayed females implanted with the pituitary tumor and in those treated with estrogen. It is suggested that these mammary tumors are the result of the action of the pituitary tumors, which apparently produce only prolactin. In 1,812 normal female rats, seven ovarian tumors (0.3%) were found, compared with 8 (5.4%) in intact females with grafted gonadotropic pituitary tumors. It is suggested that these ovarian tumors were induced by the gonadotropins produced by the grafter gonadotropic pituitary tumors. In three rats with gonadotropin-produced ovarian tumor "in situ", there were mammary tumors, two epithelial and one fibroadenoma. One mammary tumor was found in a spayed female, in which seven months after inoculation the gonadotropic and ovarian tumors weighed 8.1 and 5.4 g, respectively. The pituitary gland weighed 165 mg. In this model prolactin is also suggested as the mammo-tumorigenic factor. (26 references)

- 6642 ROLES OF RNases IN CELLULAR REGULATORY MECHANISMS. (Eng.) Levy, C. C. (Baltimore Cancer Res. Center, Baltimore, Md. 21211). *Life Sci.* 17(3):311-316; 1975.

The roles that RNases may play in the cell regulatory process are reviewed with emphasis on (a) the relation between these enzymes and transcription, and (b) the processing by RNases of large precursor molecules to their respective naturally occurring RNA forms. Either polyadenine (Poly A) or polyguanine (Poly G) is reported to be a strong competitive inhibitor of RNase activity. Spermidine reverses the inhibition. From these observations a working model can be constructed to explain both the stability and ultimate degradation of eukaryotic mRNA. Formation of an inhibitor complex between RNase and RNA-terminal Poly A would prevent the decay of the mRNA. However, the eventual destruction of the mRNA would be assured, either by the accumulation of polyamines (e.g. spermidine) or, alternatively, by the gradual reduction in size of Poly A, with the concomitant reduction of its inhibitory power. Release of the RNase from its complex with Poly A would then destroy the mRNA. Studies with large precursor ribosomal RNA (rRNA) molecules suggest that cleavage of 45S RNA is brought about by an endonuclease, and that terminal regions of the large precursor molecules are also "trimmed" by an exonuclease. When the 3'OH regions of 45S, 32S, 28S, and 18S rRNA were exposed to a nucleolar

endonuclease, the terminal regions of the precursor molecules were hydrolyzed at many times the rate of the attack on 28S and 18S rRNA. The considerable differences in hydrolytic rates support the view that the exonuclease acts to trim the terminal regions of the precursor molecules. (59 references)

- 6643 THE TALE OF TWO CHEMICALS: AN ASSESSMENT OF PRODUCT STEWARDSHIP. (Eng.) Blair, E. H. (Health and Environmental Res., U.S. Area, The Dow Chemical Co.). *Am. Paint J.* 60(9):56, 57, 60, 62-64, 66-70; 1975. (No references)

- 6644 CARCINOGENS IN INDUSTRY, WITH SPECIAL REFERENCE TO DICHLOROBENZIDINE. (Eng.) Gadian, T. (Lankro Chemicals Ltd., Eccles, England). *Chem. Ind. (London)* (19):821-931; 1975. (33 references)

- 6645 COMMENTS FOR OPENING OF DISCUSSION ON "NEOPLASTIC EFFECTS". (Eng.) Mancuso, T. F. (Grad. Sch. Public Health, Univ. Pittsburgh, Pa.). *Ann. N.Y. Acad. Sci.* 246:251-257; 1975. (No references)

- 6646 THE RAINBOW TROUT AND ITS NEOPLASMS: A FERAL FISH CONVERTED TO A CANCER RESEARCH ANIMAL. (Eng.) Ghittino, P. (Istituto Zooprofilattico Sperimentale del Piemonte e della Liguria, Via Bologna, 148, Torino, Italy 10154). *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 72-78. (61 references)

- 6647 DANGERS IN RADIOLOGY? [editorial]. (Eng.) Anonymous. *Br. Med. J.* 3(5980):396; 1975. (5 references)

- 6648 IATROGENIC CARCINOGENESIS. (Ger.) Thomas, C. (Pathologisches Institut, 78 Freiburg, Albertstrasse 19, West Germany); Auer, R. *Med. Klin.* 70(5):163-168; 1975. (30 references)

- 6649 CANCER INDUCED BY IRRADIATION. (Dan.) Visfeldt, J. (Pathologisk anatomisk Institut, Juliane Mariesvej 16, DK-2199 København Ø, Denmark). *Ugeskr. Laeger* 137(11):611-615; 1975. (12 references)

- 6650 ACTINIC CARCINOMA. (Ger.) Wiskermann, A. (Univ.-Hautklinik, 2 Hamburg 20, Narrentenstr. 52, Germany). *Strahlentherapie* 150(2):195-198; 1975. (17 references)

- 6651 THYROID CANCER: DELAYED EFFECTS OF HEAD AND NECK IRRADIATION IN CHILDREN. (Eng.) Earle, J. (Stanford Medical Center, Stanford, Calif.

- 94305). *West. J. Med.* 123(4):340; 1975. (6 references)
- 6652 CANCER AS A RISK OF MEDICAL RADIATION EXPOSURE? (Ger.) Oeser, H. (Klinikum Steglitz der Freien Universitat, D-1000 Berlin 45, Hindenburgdamm 30, West Germany). *Munch. Med. Wochenschr.* 117(31):1257-1264; 1975. (84 references)
- 6653 RADIATION RISKS IN SWITZERLAND. (Ger.) Alder, F. (Eidg. Institut fur Reaktorforschung, CH-5303 Wurenlingen, Switzerland). *Mitt. Geb. Lebensmittelunters. Hyg.* 66(1):38-44; 1975. (4 references)
- 6654 A METHOD OF RECOGNISING CARCINOGENS IN THE LABORATORY. (Eng.) Howe, J. R. (Cent. Vet. Lab., Weybridge, England). *Lab. Pract.* 24(7):457-467; 1975. (17 references)
- 6655 MYCOPLASMAS AS INFECTIOUS, CAUSATIVE OR THERAPEUTIC FACTORS IN MALIGNANT TUMORS. (Ger.) Gericke, D. (Krebsforschungslabor, Hoechst AG, D-6000 Frankfurt/M. 80, West Germany). *Munch. Med. Wochenschr.* 117(24):1041-1044; 1975. (No references)
- 6656 TEMPERATURE-SENSITIVE MUTANTS OF HERPES-VIRUSES. (Eng.) Schaffer, P. A. (Baylor Coll. Medicine, Texas Medical Center, Houston, Tex. 77025). *Curr. Top. Microbiol. Immunol.* 70:51-100; 1975. (130 references)
- 6657 NOTES ON THE PATHOGENESIS OF CERVICAL CANCER. (Ita.) Rosso, G. (Ospedale Civile S. Croce, Moncalieri, Italy); Bottino, G. *Minerva Ginecol.* 27(4):304-310; 1975. (28 references)
- 6658 IMMUNOSUPPRESSION AND NEOPLASIA. (Eng.) Schwartz, R. S. (Boston, Mass.); Penn, I. *Transplant Proc.* 7(1/Suppl. 1):899-900; 1975. (No references)
- 6659 TUMOR IMMUNOLOGY, METHODS, TECHNIQUES, AND STANDARDS FOR EVALUATION. II. MAN. (Eng.) Fefer, A. (Seattle, Wash.); Solizanu, D. *Transplant. Proc.* 7(1/Suppl. 1):897-898; 1975. (No references)
- 6660 TUMOR IMMUNOLOGY. (Eng.) Borsos, T. (Bethesda, Md.); Klein, E. *Transplant. Proc.* 7(1/Suppl. 1):895-896; 1975. (No references)
- 6661 THE CONNECTIVE TISSUE FREE CELLS IN PATHOLOGICAL PROLIFERATION OF THE EPITHELIUM AND IN TUMOUR GROWTH. (Rus.) Zhuravleva, T. B. (I. P. Pavlov First Leningrad Medical Inst., Leningrad, U.S.S.R.); Antipova, L. M. *Ark. Patol.* 37(3):3-12; 1975. (98 references)
- 6662 PATHOBIOLOGY OF NEOPLASIA: A TEACHING MONOGRAPH. (Eng.) Prehn, R. T. (Fox Chase Center for Cancer and Medical Sciences, Philadelphia, Pa. 19111); Prehn, L. M. *Am. J. Pathol.* 80(3):529-550; 1975. (15 references)
- 6663 A UNIFIED CONCEPT OF THE EPIDEMIOLOGY AND ENDOCRINOLOGY OF BREAST CANCER. (Eng.) Triedman, L. J. (Miriam Hosp., RI); Weaver, M. J. *R. I. Med. J.* 53(8):341-344, 356; 1975. (26 references)
- 6664 EPIDERMAL CHALONE--PAST TO PRESENT CONCEPT. (Eng.) Duell, E. A. (Univ. Michigan Medical Sch., Ann Arbor, Mich. 48104); Kelsey, W. H.; Voorhees, J. J. *J. Invest. Dermatol.* 65(1):67-70; 1975. (23 references)
- 6665 IMMUNOGLOBULINS AND ALLOANTIGENS ON THE SURFACE OF LYMPHOID CELLS. (Eng.) Vitetta, E. S. (Univ. Texas Southwestern Medical Sch., 5323 Harry Hines Blvd., Dallas, Tx. 75235); Uhr, J. W. *Biochim. Biophys. Acta* 415(2):253-271; 1975. (118 references)
- 6666 ROLE OF THE REGIONAL LYMPH NODES IN TUMOR IMMUNITY. (Eng.) Perez, C. A. (Washington Univ. Sch. Medicine, St. Louis, Mo. 63110); Stewart, C. C.; Wagner, B. *Interaction of Radiation and Host Immune Defense Mechanisms in Malignancy*, Conference, 5th, The Greenbrier. White Sulphur Springs, West Virginia, March 23-27, 1974. Chaired by Bond, V. P.; Hellman, S.; Order, S. E.; Suit, H. D.; Withers, H. R. Brookhaven National Laboratory Associated Universities, Inc., 1974, pp. 225-244. (51 references)
- 6667 IMMUNOSELECTION OF TUMORS. (Eng.) Zimmermann, A. (Inst. Pathology, Univ. Bern, Bern, Switzerland); Roos, B.; Hess, M. W.; Cottier, H.; Bertschmann, M. *Interaction of Radiation and Host Immune Defense Mechanisms in Malignancy*, Conference, 5th, The Greenbrier. White Sulphur Springs, West Virginia, March 23-27, 1974. Chaired by Bond, V. P.; Hellman, S.; Order, S. E.; Suit, H. D.; Withers, H. R. Brookhaven National Laboratory Associated Universities, Inc., 1974, pp. 60-74. (105 references)
- 6668 ISOLATION AND QUANTIFICATION OF LSH AND THE EVALUATION OF RELATED SERUM BASIC PROTEINS IN NORMAL ADULTS AND CANCER PATIENTS. (Eng.) Luckey, T. D. (Univ. Missouri Sch. Med., Columbia); Venugopal, B. *Ann NY Acad Sci* 249:166-176; 1975. (26 references)

- 6669 IMMUNOLOGY OF THE LYMPHOID LEUKEMIAS.
(Eng.) Gatti, R. A. (Karolinska Inst.,
Dept. Tumor Biology, Stockholm, Sweden). *Proc.
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- 6670 COMMENTS ON THE IMPORTANCE OF SOME RECENT
NEUROENDOCRINOLOGY ADVANCES. (Eng.)
Peck, W. A. (601 Elmwood Ave., Rochester, N.Y.
14642). *Arch. Intern. Med.* 135(10):1362-1363;
1975. (18 references)
- 6671 MANY MODELS FOR CELL GROWTH AND DEVELOP-
MENT. (Eng.) Shields, R. (No affiliation
given). *Nature* 257(5527):448-449; 1975. (8 refer-
ences)

- 6672 EFFECT OF SODIUM HYPOCHLORITE ON PEANUT PROTEIN ISOLATES. (Eng.) Natarajan, K. R. (Presidency Coll., Madras 600 005, India); Rhee, K. C.; Cater, C. M.; Mattil, K. F. *J. Food Sci.* 40(6):1193-1198; 1975.

The aflatoxin detoxification potential of sodium hypochlorite (NaOCl), and its effect on the color, viscosity, solubility, and amino acid composition of peanut protein isolates were investigated. Total peanut proteins were extracted from defatted peanut meal and instrumentally analyzed. An unexpected effect of the NaOCl treatment was a darkening of the protein isolates; while no specific cause for the color development was discerned, a role of the interaction of carbonyl and amino groups was suggested. The NaOCl-treated protein isolates had slightly lower solution viscosities than the untreated isolates. While both treated and untreated protein isolates had minimum nitrogen solubility around pH 5, the NaOCl treatment lowered the nitrogen solubility in the pH range 5.5-7.5 by 15-30%. While similar trends were noted, the NaOCl treatment also effected a lower solubility of the protein isolates in the presence of Ca^{2+} , Mg^{2+} , and Na^+ . Nitrogen solubility generally increased with increasing divalent cation concentration, yet was inversely correlated with Na^+ concentrations. Except for tyrosine and tryptophan; there were no evident trends in the overall amino acid composition resulting from NaOCl treatment. At 0.4% NaOCl, there was a 40% reduction in tyrosine, a 60% reduction in tryptophan, and a slight increase in glycine. In both NaOCl-treated and untreated protein isolates, phenylalanine and leucine were the predominating essential amino acids, while relatively high concentrations of arginine, aspartic acid, serine, glutamic acid, proline, and glycine were observed. The levels of cysteine acid, methionine, tryptophan, lysine, threonine, and isoleucine were comparatively low. Disc gel electrophoretic patterns illustrated several differences in the treated and untreated protein isolates, while a three-fold nitrogen fertilizer effect on nutrient composition variabilities was tabulated.

- 6673 FUNGI AND AFLATOXIN IN A BIN OF STORED WHITE MAIZE. (Eng.) Lillehoj, E. B. (Agric. Res. Serv., Peoria, Ill.); Fennell, D. I.; Hara, S. *J. Stored Prod. Res.* 11(1):47-51; 1975.

Samples of maize (*Zea mays* L.) from discolored spots in the surface layer of stored grain in a southeast Missouri bin were examined for variation in microbial profile and for the presence of aflatoxin. Comparisons were made with samples of non-discolored maize from the same bin. Deteriorated test kernels showed a high incidence of *Penicillium*, *Aspidia*, *Mucor*, *Rhizopus* and *Fusarium* sp., as well as bacteria and yeasts. *Aspergillus* species were also frequently observed; *A. Flavus*, the most common species, was found in some kernels from all fractions. In one sample of discolored maize 80% of the kernels contained *A. flavus* and the sample had 0.40 ppm aflatoxin B₁. Other fractions exhibited extensive discoloration but no aflatoxin. Excessive moisture accumulation in localized regions

of the surface layer of stored maize was responsible for the rapid fungal development and subsequent deterioration of the maize.

- 6674 THE MUTAGENIC EFFECT OF PESTICIDES ON *ESCHERICHIA COLI* WP2 *try*⁻. (Eng.) Nagy, Z. (Simmelweis Univ. Medical Sch., Puskin utca 9, H-1088 Budapest, Hungary); Mile, I.; Antoni, F. *Acta Microbiol. Acad. Sci. Hung.* 22(3):309-314; 1975.

Thirty pesticides commercially available in Hungary and three well-known chemical mutagens were applied (as a single 1-3 mg crystal or as a 20-25 μl micro-drop) to agar plate cultures of *her*⁺ and *her*⁻ derivatives of *Escherichia coli* WP2 *try*⁻ strain. After incubation, the plates were examined by the spot test technique for a relative increase in the number of reverse mutations. Of the pesticides tested, dimethyl-2,2-dichlorovinyl-phosphate (DDVP), captan, and folpet were markedly mutagenic and tetradifon exhibited mutagenic activity in some experiments. The mutagenic effect of the latter agent was variable and not consistently reproducible. None of the other 26 compounds induced reverse mutations. The mutagenicity of captan and, to a lesser extent, of DDVP was independent of the ability of the bacterial repair system; the agents were mutagenic for both the *her*⁺ and *her*⁻ strains. Folpet and tetradifon were mutagenic only for the repair deficient strain. The three known chemical mutants, N-methyl-N'-nitro-soguanidine, N-nitroso-N-methylurethane, and acridinium chloride, were strongly mutagenic in both the *her*⁺ and *her*⁻ strains.

- 6675 A STUDY OF A TOXIC EFFECT OF THE STRAINS OF *ASPERGILLUS FLAVUS* FUNGI METABOLITES, ISOLATED FROM SOVIET-GROWN CEREALS. (Rus.) Mechkov, N. V. (Inst. Nutrition, Acad. Medical Sciences of the USSR, Moscow, USSR); Bogoroditskaia, V. P. *Vopr. Pitan.* (4):59-62; 1975.

The acute toxicity of extracts of pure cultures of 16 *Aspergillus flavus* strains isolated from cereals grown in the USSR was studied in ducklings, chickens, and young albino rats by oral administration. Animals fed extracts of the American strain NRRL No. 2999, an aflatoxin-producing strain, were used as control. Extracts of strain No. 104, isolated from winter rye, were found to be toxic in all animals, while extracts of the other strains caused no toxic changes. A metabolite in this extract showed a fluorescence characteristic for aflatoxin. This extract caused the death of most animals within a few days. Diffuse fatty degeneration of the liver (fatty infiltration of the parenchyma with proliferation of the epithelium of the bile ducts) was observed in all animals. Ascites was found in 3 of 7 rats. Significantly reduced cytoplasmic RNA and glycogen levels in the hepatocytes were observed in all cases. The morphological changes and toxic effects were analogous to those observed in the control group.

- 6676 ASSOCIATION OF SALMONELLA MUTANTS WITH GERM-FREE RATS: SITE SPECIFIC MODEL TO DETECT CARCINOGENS AS MUTAGENS. (Eng.) Wheeler,

L. A. (Beth Israel Hosp., Boston, Mass. 02215); Carter, J. H.; Soderberg, F. B.; Goldman*, P. *Proc. Natl. Acad. Sci. USA* 72(11):4607-4611; 1975.

An association of the histidine auxotroph of *Salmonella typhimurium* (strain TA1538) within the gastrointestinal tract of otherwise germfree male Sprague-Dawley rats was maintained during periods of observation lasting as long as seven months. The bacteria were found at levels exceeding $10^7/g$ in the forestomach and at levels greater than $10^8/g$ in the lower bowel and in the feces. Approximately 10^4 bacteria/g were found in the posterior stomach and in the upper small intestine. The association of the *salmonella* mutants was maintained when the bacterial association was increased by the addition of other bacteria characteristic of the gastrointestinal flora (*Laetobacillus plantarum*, *Streptococcus fecalis*, and *Bacteroides fragilis*). Carcinogenic amines (3,2'-dimethyl-4-aminobiphenyl, 4 mg/day, two days; 2-nitrofluorene, 3.4 mg/day, three days; 2-acetylaminofluorene, 3.6 mg/day, five days; 4-nitrobiphenyl, 50 mg/day, three days; and 4-nitrobenzoic acid, 25 mg/day, four days), which cause strain TA1538 to revert to histidine independence in Ames' *in vitro* assays, increased the number of revertants in the feces when fed to the salmonella-associated rats. In contrast, the number of revertants in the feces did not increase when the rats were fed structurally related compounds which were not mutagenic to the bacteria *in vitro* and for which no evidence of carcinogenicity exists. Sacrifice of rats after feeding the carcinogen 2-nitrofluorene indicated that the number of revertants was increased in the cecum and colon as well as in the feces. The apparent proximity of the bacterial mutagenic response to the location of the tumor response in the colon suggests that the rat gastrointestinal tract association with the histidine auxotroph may provide a useful model for further investigation of the possible association between bacterial mutagenesis and carcinogenesis within the gastrointestinal tract. In addition, with this model it may be possible to evaluate selectively the effects of various constituents of the flora on the activation of compounds provoking the revertant response.

6677 MUTANT HAMSTER CELLS EXHIBITING A PLEIOTROPIC EFFECT ON CARBOHYDRATE METABOLISM. (Eng.) Sun, N. C. (Univ. Michigan Med. Sch., Ann Arbor); Chang, C. C.; Chu, E. H. Y. *Proc. Natl. Acad. Sci. USA* 72(2):469-473; 1975.

The growth behavior and the biochemical and genetic characteristics of several of 67 galactose negative (Gal⁻) mutants of Chinese hamster lung (V79) cells produced by treatment with 5-bromodeoxyuridine and black light are described. Unlike the parental cells, these mutants could not utilize exogenous galactose, mannose, fructose, galactose-1-phosphate, glucose-1-phosphate, or glucose-6-phosphate for growth. Normal galactose uptake by the mutants was demonstrated with ^{14}C -galactose. All of the 27 mutants tested reverted spontaneously, regaining their ability to utilize galactose. Enzyme studies in the mutants revealed

that phosphoglucomutase was sharply reduced compared to the parental cells (mean 38%), as was NADP-dependent isocitrate dehydrogenase (mean 32%). Galactokinase, epimerase, and UDPglucose pyrophosphorylase were somewhat less active than in parental cells, while galactose-1-phosphate uridylyltransferase appeared normal. In temperature-sensitive Gal⁻ mutants grown at permissive temperature or in complementing intra- and interspecific cell hybrids, enzyme activities were restored to normal, accompanied by a regained ability to utilize the particular hexoses or their monophosphates. It is postulated that the change from Gal⁺ to Gal⁻ phenotype in hamster cells might be due to mutations at a regulatory gene locus, or at a yet unknown locus with enzymic defect that causes secondary metabolic imbalances.

6678 FORMATION OF INDOLEACETIC ACID BY INTES-TINAL ANAEROBES. (Eng.) Chung, K.-T. (Dept. Chemistry, Univ. Maryland, College Park, Md. 20742); Anderson, G. M.; Fulk, G. E. *J. Bacteriol.* 124(1):573-575; 1975.

Filtrates from cultures of 23 intestinal anaerobes were screened by thin-layer chromatography for the presence of indoleacetic acid. Two possible pathways for the conversion of tryptophan to indoleacetic acid were proposed; 1) the formation of indolepyruvic acid by transamination with α -ketoglutarate followed by decarboxylation; or 2) decarboxylation to tryptamine followed by deamination and oxidation of this amine, which would be inhibited by iproniazid, a monoamine oxidase inhibitor. To determine the correct pathway, each culture was grown in an anaerobic tryptophan-free medium. The tests included incubation of washed cells with a) tryptophan (100 mg), b) tryptophan + α -ketoglutarate (50 mg), c) tryptophan + α -ketoglutarate + iproniazid (35 mg), d) tryptophan + iproniazid, and e) buffer only. After incubation, the supernatants from the test cells were used for the determination of indoleacetic acid by gas chromatography. The results showed that α -ketoglutarate stimulated the formation of indoleacetic acid, 1.08 $\mu g/mg$ dry cells as compared to 0.33 $\mu g/mg$ dry cells with tryptophan alone. Also iproniazid did not inhibit indoleacetic acid formation, thus it was assumed that the pathway was *via* indolepyruvic acid.

6679 GROWTH AND STRUCTURAL PROPERTIES OF EPITHELIAL CELL CULTURES ESTABLISHED FROM NORMAL RAT LIVER AND CHEMICALLY INDUCED HEPATOMAS. (Eng.) Weinstein, I. B. (Coll. Physicians and Surgeons, Columbia Univ., New York, N.Y. 10032); Orenstein, J. M.; Gebert, R.; Kaighn, M. E.; Stadler, U. C. *Cancer Res.* 35(1):253-263; 1975.

Epithelial cultures from adult rat liver and from rat hepatomas induced *in vivo* with aromatic amine carcinogens were compared by light and electron microscopy and by growth properties in liquid medium and in agar. The morphology and growth patterns of these cultures have characteristics of epithelial rather than fibroblast cells. The criteria generally used to score for transformation of fibroblasts were not satisfactory for distin-

guishing normal epithelial cells from hepatoma cells in culture. Growth in agar, however, provides a simple and objective method of scoring for transformed epithelial cells because only the tumorigenic cells grow in agar. Since none of the normal cultures had hydrocortisone-inducible tyrosine aminotransferase, definitive evidence was lacking that they are derived from liver parenchymal cells. The outstanding feature in the ultrastructure of the hepatoma cells in culture was the presence of type A and C viral particles. Five hepatoma cultures and a spontaneously transformed normal liver cell line were positive for these particles. Five independently isolated cell cultures from normal adult rat liver were negative. The viral particles were detected in cultures from transplantable and primary hepatomas, and not in cultures from normal adult liver; attempts to infect normal cultures from particles from hepatoma cells were negative. These observations indicate that the viral particles seen in hepatoma cultures are due to inactivation of latent viruses rather than to *in vitro* contamination.

- 6680 RING- AND *N*-HYDROXYLATION OF 2-ACETAMIDOFLUORENE BY RAT LIVER RECONSTITUTED CYTOCHROME P-450 ENZYME SYSTEM. (Eng.) Lotlikar, P. D. (Temple Univ. Sch. Medicine, Philadelphia, Pa. 19140); Zaleski, K. *Biochem. J.* 150(3):561-564; 1975.

The *N*- and ring-hydroxylation of 2-acetamidofluorene were studied with a reconstituted cytochrome P-450 enzyme system from microsomal fractions of liver from both control and 3-methylcholanthrene-pretreated (100 mg/kg, ip) male Sprague-Dawley rats. Bacterial protease treatment and Triton X-100 solubilization were two important steps for partial purification of the cytochrome P-450 fraction. Both cytochrome P-450 and NADPH-cytochrome *c* reductase fractions were required for optimum *N*- and ring-hydroxylation activity. Hydroxylation activity was determined by the source of cytochrome P-450 fraction; cytochrome P-450 fraction from pretreated animals was severalfold more active than the fraction from controls. Formation of *N*-hydroxylated metabolites with reconstituted systems from both control and pretreated animals was greater than that with their respective whole microsomal fractions. The authors suggest that this might have been due to the presence of small amounts of Triton X-100 in the cytochrome fraction.

- 6681 COMPARATIVE TOXICITY OF *N*-HYDROXY-2-ACETYLAMINOFLUORENE IN SEVERAL STRAINS OF RATS. (Eng.) Irving, C. C. (Univ. Tennessee Center for Health Sciences, Memphis, Tenn. 38104). *Cancer Res.* 35(11/Part 1):2959-2961; 1975.

The toxicity of *N*-hydroxy-2-acetylaminofluorene was compared in male and female Holtzman, Sprague-Dawley, Wistar, and Fischer rats. The LD₅₀ was determined and compared with data obtained for *N*-hydroxy-2-acetylaminofluorene sulfotransferase activity. All animals were given *N*-hydroxy-2-acetylaminofluorene ip (7.5 ml/kg). Sulfotransferase

activity was determined in the 105,000 × *g* supernatant of liver homogenate by a procedure in which the unstable *N*-hydroxy-2-acetylaminofluorene-*N*-sulfate formed was trapped by reaction with methionine. Male Sprague-Dawley rats were 6 - 7 times more susceptible than females to the acute toxic effects of the single injection of *N*-hydroxy-2-acetylaminofluorene. The *N*-hydroxy compound was equally toxic in male and female Fischer rats and about twice as toxic to male as to female Wistar rats. A negative correlation between the 50% lethal dose of *N*-hydroxy-2-acetylaminofluorene and hepatic *N*-hydroxy-2-acetylaminofluorene sulfotransferase activity was found. These data substantiate earlier indications that the level of the liver sulfotransferase is an important factor in determining the degree of toxicity of *N*-hydroxy-2-acetylaminofluorene. It is suggested that the reported sex difference in the hepatocarcinogenicity of *N*-hydroxy-2-acetylaminofluorene might be peculiar to the Sprague-Dawley rat.

- 6682 LOCALIZATION IN THE CELL CYCLE OF THE ANTIMITOTIC ACTION OF THE PYRROLIZIDINE ALKALOID, LASIOCARPINE AND OF ITS METABOLITE, DEHYDROHELIOTRIDINE. (Eng.) Samuel, A. (Animal Health Res. Lab., Private Bag No. 1, P.O., Parkville, Victoria, 3052 Australia); Jago, M. V. *Chem. Biol. Interact.* 10(3):185-197; 1975.

The antimitotic action of the pyrrolizidine alkaloid lasiocarpine on (Wistar) rat liver parenchyma was investigated using as the experimental model the wave of mitosis produced in liver by a single dose of thioacetamide (60 mg/kg). A single dose of lasiocarpine (15.6 mg/kg, ip) administered two wk before the thioacetamide, almost completely inhibited the mitotic wave without inhibiting to the same extent the preceding wave of DNA synthesis. If lasiocarpine was given more than 13 hr before the determination of the mitotic index, mitosis was almost completely inhibited. Inhibition decreased as the interval between injection and measurement of mitosis decreased. By the use of selective inhibitors and radioisotope labelling, the location of the mitotic block was found to be either in S or early in G₂ phase. The mitotic wave was similarly inhibited by pretreatment of the rats with a single injection of dehydroheliotridine.

- 6683 COMPARATIVE KARYOMETRIC STUDIES ON SMALL PSEUDOLOBULI AND HEPATOMAS IN THIOACETAMIDE INDUCED LIVER CIRRHOSIS. (Eng.) Bader, G. (Bezirkskrankenhaus Rostock-Sudstadt, DDR--25 Rostock, Am Sudring, East Germany); Bader, N. G.; Busch, B.; Stiller, K. J. *Exp. Pathol. (Jena)* 10(5/6):241-244; 1975.

Karyometric studies on pseudolobuli and hepatomas during the late phase (6th-9th mo) of thioacetamide (TAA)-induced liver cirrhosis are reported. Ten hepatomas of three rats were evaluated after 8-9 mo of TAA intoxication (25 mg/kg/day). In small nodular liver cirrhosis, bright yellowish hepatomas were observed between the pseudolobuli. The mean values of the mitotic indices, as well as the percentages of binucleated liver cells in hepatomas and pseudolobuli, were similar. The mitotic index

of the hepatomas and pseudolobuli was subnormal, "indicating cell proliferation characterized by amitoses." DNA-Feulgen photometry revealed that hepatomas were diploid whereas pseudolobuli were tetraploid. In the pseudolobuli, the ploidy border of diploid liver cells is 7.7 μM , in hepatomas it is 9.3 μM . In hepatomas, the number of nuclei per unit area (0.63 mm^2) was somewhat higher than that in pseudolobuli.

- 6684 THE INHIBITION OF GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE BY BENZ(a)ANTHRACENE AND ITS DERIVATIVES AFTER EXPOSURE TO LABORATORY LIGHTING. (Eng.) Grubbs, C. J. (Univ. Tennessee Cent. Health Sci., Memphis); Hutcheson, E. T.; Wood, J. L. *Chem. Biol. Interact.* 10(3):173-183; 1975.

The inhibition of glyceraldehyde-3-phosphate dehydrogenase (GPDH) and lactic acid dehydrogenase (LDH) by colloidal dispersions of polycyclic aromatic hydrocarbons and the effects of light, pH, and oxygenation on the inhibition were investigated. Inhibition of GPDH was 100% after one hr with 7,12-dimethylbenz(a)anthracene (0.1 $\mu\text{mole/ml}$) at pH 9 under ordinary light; somewhat less striking inhibition was observed with benz(a)anthracene, 7-methylbenz(a)anthracene, 12-methylbenz(a)anthracene, and methylcholanthrene. LDH was inhibited approximately 80% in five hr under similar conditions. Inhibition of either enzyme was absent or very slight when the incubations were carried out in the dark. Light-activated 7-methyl derivatives of 12-methylbenz(a)anthracene were also inhibitory. As little as one min exposure to light was sufficient to produce a measureable inhibition of GPDH by 7-methoxymethyl-12-methylbenz(a)anthracene. Inhibition was less pronounced at pH 7.4 than at 9.0. Inhibition was directly related to the concentration of the hydrocarbon, and required the presence of oxygen in the incubation medium. A small but significant effect of light on the inhibition of the enzymes by K-region epoxides was observed: protein binding of the epoxides did not correlate well with the inhibition. The active form of light-activated 7-methoxymethyl-12-methylbenz(a)anthracene decayed slowly over more than 25 days. The importance of protecting reactions involving these compounds and their derivatives from light is emphasized.

- 6685 RIBOSOMAL APPARATUS OF LIVER CELLS IN CARCINOGENESIS INDUCED BY 4-DIMETHYL-AMINOAZOBENZENE. (Rus.) Berdinskikh, N. K. (Inst. Oncol. Probl., Kiev, USSR); Bykorez, A. I.; Kozak, V. V.; Kulik, V. A.; Lyalyushko, N. M. *Biokhimiia* 40(1):40-44; 1975.

The authors studied biochemically the condition of the ribosomal apparatus of liver cells of rats fed the carcinogen 4-dimethylaminobenzene (DAB) at a dose of 12 mg/day/animal. The animals were kept on a diet of polished rice (15 g/day) for 1-10 days, 1-2 mo, 3-4 mo, 5 mo from the start of DAB feeding. Liver cells from hepatomas developing as the result of DAB administration were electron microscopically studied and changes in the endoplasmic reticulum in

the form of endoplasmic membrane disorganization (swelling and fragmentation) and simultaneous separation of ribosomes were revealed. In the first days of DAB administration, it was found that protein synthesis of polyribosome preparations from rat liver cells was reduced, the number of membrane-bound ribosomes was decreased, that of free ribosomes (located in the cytoplasm) increased. While in healthy control animals the ratio of membrane-bound to free ribosomes was about 67.3%:35.3%, it changed after some days of DAB treatment to 38.1%:66.1%; this trend continued during all phases of DAB carcinogenesis. It can be assumed that the interference by carcinogens in the hormone-controlled linkage of ribosomes and endoplasmic membrane is an important condition of chemical carcinogenesis which alters the regulation of protein biosynthesis in the cytoplasm.

- 6686 THE USE OF HIGH PRESSURE LIQUID CHROMATOGRAPHY TO STUDY CHEMICALLY INDUCED ALTERATIONS IN THE PATTERN OF BENZO(a)PYRENE METABOLISM. (Eng.) Freudenthal, R. I. (Battelle Columbus Lab., 505 King Ave., Columbus, Ohio 43201); Leber, A. P.; Emmerling, D.; Clarke, P. *Chem. Biol. Interact.* 11(5):449-458; 1975.

The metabolism of radiolabeled benzo(a)pyrene by control, by 3-methylcholanthrene-induced and by 1,1,1-trichloropropene-2,3-oxide-inhibited rat liver microsomes was measured. Male Sprague-Dawley rats were sacrificed 24 hr after an ip injection of 40 mg 3-methylcholanthrene in corn oil. Liver microsomes were prepared by centrifugation of the liver homogenate for 20 min at $10,000 \times g$, followed by centrifugation of the resulting supernatant for 60 min at $105,000 \times g$. Benzo(a)pyrene was incubated with 7 mg microsomal protein in a reaction mixture containing 4.2 μM NADP, 70 μM glucose-6-phosphate, 175 μM MgCl_2 , 7 U glucose-6-phosphate dehydrogenase, and 700 nM double-labeled benzo(a)pyrene ($[^3\text{H}]$ -benzo(a)pyrene and $[^{14}\text{C}]$ -benzo(a)pyrene) in 50 μl methanol. In some cases, the incubation mixture also contained 5×10^{-4} M 1,1,1-trichloropropene-2,3-oxide. After 20 min incubation, aliquots of the incubation mixture were analyzed by fluorometric, radiometric, and high-pressure liquid chromatographic assays. Nuclear magnetic resonance spectra were obtained for each chromatographic fraction. Eight benzo(a)pyrene metabolites were identified by high-pressure liquid chromatography. 3-Hydroxybenzo(a)pyrene was the major metabolite. Significant amounts of the 9,10-dihydrodiol and of the quinone metabolites were also present. In the 3-methylcholanthrene-induced microsome preparations, there was an increase in highly fluorescent metabolites (3-hydroxy and 9-hydroxy fractions), and a substantial increase in the concentration of the three dihydrodiols (7,8-, 4,5-, and 9,10-dihydrodiols). When the epoxide hydrolase activity was inhibited by 1,1,1-trichloropropene-2,3-oxide, the formation of the dihydrodiols was totally inhibited resulting in an increased formation of 3-hydroxybenzo(a)pyrene and 9-hydroxybenzo(a)pyrene. Nuclear magnetic resonance spectra revealed that the 3-hydroxybenzo(a)pyrene was greater than 90% pure, but the

9-hydroxy fraction contained a number of metabolites having essentially the same retention times. Significant differences in the total measurable metabolism of benzo(a)pyrene resulted from the use of three assay procedures. The substantial increase in the 9-hydroxy fraction (366%) and relatively small increase in the 3-hydroxy benzo(a)pyrene concentration (38%) as a result of 1,1,1-trichloropropene-2,3-oxide-inhibition suggests that the components of the 9-hydroxy metabolite fraction are readily formed *via* spontaneous rearrangement.

- 6687 THE BENZO(a)PYRENE DEOXYRIBONUCLEOSIDE PRODUCTS ISOLATED FROM DNA AFTER METABOLISM OF BENZO(a)PYRENE BY RAT LIVER MICROSOMES IN THE PRESENCE OF DNA. (Eng.) King, H. W. S. (Inst. Cancer Res.); Thompson, M. H.; Brookes, P. *Cancer Res.* 35(5):1263-1269; 1975.

Rat liver microsomes (36 hr after 3 mg of 3-methylcholanthrene, ip) were used to catalyze the binding of tritium-labeled benzo(a)pyrene [^3H]BP to DNA prepared from calf thymus. Sonically disrupted and heated DNA gave the highest level of BP binding (20 pmoles/mg DNA) and of aryl hydrocarbon hydroxylase (AHH) activity (2-fold that of microsomes alone) and was used for further experiments. Enzymic degradation of this DNA to deoxyribonucleosides, followed by separation of the products by Sephadex LH20 column chromatography, revealed two major products. One of these (peak A) was shown to be the same as that obtained from DNA isolated from mouse embryo cells exposed to [^3H]BP. Neither product resembled those obtained from DNA that had been caused to react with benzo(a)pyrene 4,5-oxide (K-region epoxide). The AHH showed parallel increases with microsome-catalyzed hydrocarbon binding. Inhibitors of the enzyme epoxide hydrolase increased this binding but caused the loss of peak A. A model is proposed of the mechanism of benzo(a)pyrene metabolism and DNA binding.

- 6688 EFFECT OF STABILIZERS ON DIAMINO BENZIDINE REACTIONS OF MITOCHONDRIA. (Eng.) Litwin, J. A. (Inst. Biomorphology, Medical Acad., Kopernika 7 PL-31-034 Krakow, Poland). *Histochemistry* 44(4): 349-355; 1975.

The effect of various stabilizers, 0.9% NaCl, 7.5% sucrose, and 7.5% polyvinyl pyrrolidone (PVP), on reactions of mitochondria with fresh and photo-oxidized diaminobenzidine (DAB) was investigated. The tissues used were cardiac muscle and kidney cortex from rabbit, rat, mouse, and rabbit gastric mucosa. These were tested either fresh, fixed with buffered 4% paraformaldehyde for one hour, or fixed with buffered 2.5% glutaraldehyde overnight. NaCl and PVP abolished the DAB staining of mitochondria when incubated with tissue alone. When exogenous cytochrome c or oxidized DAB was present in the incubation medium, NaCl had no inhibitory effect; however, PVP considerably decreased or abolished the intensity of all reactions of DAB with mitochondria. Sucrose (7.5%) allowed an intense reaction under all conditions. The mechanism of the observed effects is discussed.

- 6689 SACCHARIN: LACK OF CHROMOSOME-DAMAGING ACTIVITY IN CHINESE HAMSTERS *IN VIVO*. (Eng.) van Went-de Vries, G. F. (Lab. Pharmacol., Natl Inst. Public Health, Bilthoven, Netherlands); Kragten, M. C. T. *Food Cosmet. Toxicol.* 13(2):177-183; 1975.

Chromosomes in bone-marrow cultures from 20 Chinese hamsters given high doses of saccharin were studied. The test animals and a group of 20 controls were ip injected with 0.25 ml of pertussis vaccine, containing 16×10^9 bacteria/ml, to increase the population of mitotic cells. The animals were then given 1.5 g/kg/day of sodium saccharinate by gastric intubation on days 2, 3, and 4 after pertussis injection. The saccharin contained 6-7 impurities including 0.5% o-toluenesulphonamide. Phytohemagglutinin (PHA) was administered on day 6 and bone marrow cultures were taken on day 8 after pertussis injection. In each culture, 50 metaphases were analyzed. No statistically significant increases in the number of polyploid or aneuploid cells or in structural chromosome abnormalities were seen in comparison with the controls. Neither the saccharin nor its impurities caused chromosome abnormalities in this experiment, suggesting that saccharin has no *in vivo* chromosome-damaging effect on mitotic cells.

- 6690 EFFECTS OF NITROGEN DIOXIDE AND 3-METHYLCHOLANTHRENE ON PULMONARY ENZYMES. (Eng.) Law, F. C. P. (Coll. of Pharmacy and Sch. of Dentistry, Univ. of Michigan, Ann Arbor, Mich. 48104); Drach, J. C.; Sinsheimer, J. E. *J. Pharm. Sci.* 64(8):1421-1422; 1975.

Guinea pig phenol-O-methyltransferase, catechol-O-methyltransferase, and benzpyrene hydroxylase activities were examined after nitrogen dioxide (40 or 70 ppm, two hours) or 3-methylcholanthrene (20 mg/kg, ip) treatment. 3-Methylcholanthrene increased benzpyrene hydroxylase activity about 2-fold (from 0.22 to 0.42 nM/g tissue). However, neither microsomal phenol-O-methyltransferase nor microsomal and supernatant catechol-O-methyltransferase activities were affected. None of the pulmonary enzyme activities was altered after two hours of exposure to either concentration of nitrogen oxide.

- 6691 INDUCTION OF MALIGNANT LYMPHOMAS IN SWISS MICE BY N-NITROSO COMPOUNDS FORMED *IN VIVO*. (Eng.) Borzsonyi, M. (Natl. Inst. Hyg., Budapest, Hungary); Csik, M. *Int. J. Cancer* 15(5):830-838; 1975.

The effects of methyl-2-benzimidazole carbamate (MBC) and sodium nitrate was studied in 166 inbred Swiss mice. The mice were divided into groups, designated A to F, as follows: A, ten females; B, ten pregnant females; C, ten males; D and E, ten females each; and F, 78 females and 38 males. Groups A-D were given MBC (250 mg/kg, intragastrically) twice weekly. Groups E and F were given no MBC. Groups A, B, C, and E received 0.5% NaNO_2 in drinking water. Tumors appeared 82-164 days after the onset of the experiment. Ten of the 30 mice treated with MBC and NaNO_2

developed malignant lymphomas. Animals treated with MBC alone (group D), or NaNO_2 alone (group E) did not develop tumors. Of the 116 controls, three mice developed tumors; they were mammary adenocarcinoma, lymphosarcoma, and renal adenoma. In the offspring of pregnant mice (group B) there was an increased incidence of lymphosarcoma. A-type virus particles were demonstrated within the tumor cells by electron microscopy. The results suggest that *in vivo* nitrosation, by NaNO_2 of MBC or one of its derivatives produces carcinogen responsible for lymphoma induction in mice. The author suggests that this nitrosation of MBC or its derivative may occur only *in vivo*.

- 6692 URETHAN (ETHYL CARBAMATE) AS A COSOLVENT OF DRUGS COMMONLY USED PARENTERALLY IN HUMANS. (Eng.) Nomura, T. (Osaka Univ. Medical Sch., Dojima-hamadori, Fukushima-Ku, Osaka 553, Japan). *Cancer Res.* 35(10):2895-2899; 1975.

Sixty-three drugs used parenterally in Japan and 72 cosmetics were analyzed for urethan content. Four products for parenteral use showed components chromatographically identical to urethan. Grelan injection (pyrabital and aminopyrine), Noblon-A injection (pyrabital, chlorpromazine hydrochloride, and diphenhydramine), Noblon-B injection, and C-Noblon injection (pyrabital, surpyrine, chlorpromazine hydrochloride, promethazine hydrochloride, and 8-chlorotheophylline) contain urethan as a cosolvent, because pyrabital is insoluble in water. Lung tumors were induced ($p < 0.001$) with a Grelan injection (0.002 ml/g, sc, in ICR/Jcl mice). Long-term followup of patients exposed to urethan, and examination of other drugs is necessary to evaluate possible carcinogenic effects of urethan in humans.

- 6693 EXPERIMENTAL EVIDENCE. (Eng.) Mohr, U. (Medizinische Hochschule Hannover, 3000 Hannover-Kleefeld, Karl-Wiechert-Allee 9, West Germany). *Proc. Int. Cancer Congr.* 11th. Vol. 2 (Chemical and Viral Oncogenesis). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 135-138.

In order to study transplacental carcinogenesis, diethylnitrosamine (DEN), 20 mg/kg, was administered to female Syrian golden hamsters on the 15th day of pregnancy. Dose did not increase maternal or fetal mortality or cause teratogenesis, and delivery and lactation were normal. Tracheal papillary tumors appeared in 42% of young by the 25th wk after birth. Similar tracheal neoplasms were observed in 72% of the mothers. If litters of treated and untreated mothers were exchanged immediately after birth, only the young of treated mothers developed tracheal tumors. Newborn did not have neoplasms is a single 45 mg/kg sc dose of DEN was given to pregnant hamster on the first to eleventh day of pregnancy. Same dose given between the 12th and 15th day did produce respiratory tract neoplasms in offspring, and the tumor rate increased from 45% to 95% in this time period. The tracheal epithelium of fetal hamsters is composed of a single

layer of regular cells up to the 12th day of gestation. It is concluded that a definite degree of differentiation must exist for fetal epithelium to react to the carcinogen DEN.

- 6694 FOCI OF ALTERED LIVER CELLS INDUCED BY A SINGLE DOSE OF DIETHYLNITROSAMINE AND PARTIAL HEPATECTOMY: THEIR CONTRIBUTION TO HEPATOCARCINOGENESIS IN THE RAT. (Eng.) Scherer, E. (Department of Biochemistry, Antoni van Leeuwenhoek-Huis, The Netherlands); Emmelot, P. *Eur. J. Cancer* 11(3):145-154; 1975.

The foci of atypical liver cells (islands) produced by diethylnitrosamine (DENA) as tumor precursors were studied using female Sprague Dawley rats. The amounts of DENA required to arrive at liver carcinoma following daily administration of relatively non-toxic doses of DENA (2.4mg/kg) started at various times after the priming treatment, were measured. The contribution of an initial 20 mg/kg dose of DENA to the carcinogenic process was enhanced significantly by prior partial hepatectomy (these two treatments = the priming treatment) as well as by the time elapsed between the priming treatment and the subsequent installment of 2.4 mg DENA/kg/day (by stomach tube). The positive correlation between the amount of island tissue induced by 20 mg DENA/kg and the latter's contribution to the carcinogenic process indicates that island cells induced by a single subcarcinogenic dose may represent the first morphologically altered cell stage in liver carcinogenesis.

- 6695 EARLY ALTERATIONS IN PLASMA ESTERASES WITH ASSOCIATED PATHOLOGY FOLLOWING ORAL ADMINISTRATION OF DIETHYLNITROSAMINE AND BUTYLATED HYDROXYTOLUENE SINGLY OR IN COMBINATION. (Eng.) Tyndall, R. L. (Medical Div., Oak Ridge Associated Universities, Oak Ridge, Tenn.); Colyer, S.; Clapp, N. *Int. J. Cancer* 16(1):184-191; 1975.

Plasma esterases in BALB/c mice fed butylated hydroxytoluene (BHT) or diethylnitrosamine (DENA) were analyzed for alterations reflective of the early action of these compounds. The mice were placed in one of four groups: (a) 60 mice fed 0.75% BHT in diet, were killed after 3, 10, or 20 wk; (b) 40 mice fed 0.75% BHT in diet plus DENA in drinking water for seven weeks beginning three weeks after initiation of BHT treatment were killed at 10 or 20 wk after initiation of treatment; (c) 40 mice given DENA for seven weeks; and (d) untreated controls. Esterase analysis was accomplished by vertical flat-bed, discontinuous electrophoresis in gradient pore-size gels. Plasma esterase activity was enhanced within three weeks after feeding BHT. Other esterase changes, different from those in BHT-treated animals were also apparent during exposure to DENA (7-8 mg/kg/day). Interference with these DENA esterase alterations was apparent in plasma of mice treated concomitantly with both DENA and BHT. Esterase changes resulting from either the carcinogen or antioxidant exposure preceded the overt histologically detected changes induced by these compounds. The early esterase changes and subsequent tumorigene-

sis resulting from DENA exposure were more severe in female mice. The same electrophoretic bands primarily affected by DENA-treatment in this study were previously reported to represent testosterone-related esterases; this fact, together with the sex-dependency of the severity of the esterase and subsequent pathologic alterations, suggests an endocrine involvement in DENA carcinogenesis.

- 6696 α -ACETOXY-DIMETHYLNITROSAMINE: A PROXIMATE METABOLITE OF THE CARCINOGENIC AMINE. (Eng.) Fahmy, O. G. (R. Cancer Hosp., London, England); Fahmy, M. J.; Wiessler, M. *Biochem. Pharmacol.* 24(10):1145-1148; 1975.

The mutagenic properties of a series of related N-methyl- and N-ethyl-N-nitrosamine derivatives with various intrinsic or potential reactive centers were investigated. α -Acetoxy-dimethylnitrosamine (AcODMN) exerted identical genetic effects as the unsubstituted parent, but at lower molarity, indicating a precursor characteristic. The substituted compound was completely sterilized at 5.0 mM, whereas parent affected fertility only 10-20%. The two compounds exerted the same mean biologic activity on the same section of testes at molecular ratio of 1:10 favoring AcODMN. They also induced identical mutation frequencies with respect to specific effects on the RNA genes and the non-specific sex-linked recessives. The mutation ratio (per 10^3) was 143.5 for DMN and 148.2 for AcODMN. These similarities indicate an identical pattern of cell stage response. The mature sperm was not affected by either compound. The ester required further activation and was considered the amine proximate, not ultimate, genetic effector metabolite. The two compounds also gave comparable frequencies of mosaic mutants among corresponding mutation classes and germ cell stage implying a similar molecular mode of action. Both compounds also gave the same rDNA selectivity index; 2.81 for DMN and 2.79 for AcODMN. It was concluded that AcODMN was a proximate metabolite of DMN.

- 6697 REACTION OF SODIUM NITRITE WITH DIMETHYLGLYCINE PRODUCES NITROSOSARCOSINE. (Eng.) Friedman, M. A. (Med. Coll. Virginia, Richmond). *Bull. Environ. Contam. Toxicol.* 13(2):226-232; 1975.

The nitrosation products of dimethylglycine in the presence of sodium nitrite were studied in a non-enzymic acidic aqueous system at 37 C and in isolated mouse stomachs. The *in vitro* reaction mixture contained 1.5 ml of 2 M dimethylglycine and 0.5 ml of 2 M sodium nitrite. The pH was adjusted to 1.0-4.0 with NaOH. Product identification was made by nuclear magnetic resonance spectra. Nitrososarcosine and dimethylnitrosamine (DMN) were identified as the products in this system. The ratio of nitrososarcosine to DMN varied (4-49) inversely with pH. Thin layer chromatography was used to identify nitrososarcosine as the reaction product in six isolated mouse stomachs injected intraluminally with 0.1 ml 14 C-dimethylglycine (10 μ Ci/ml); a 4-fold increase in the amount of product formed occurred when 0.1 ml of 8 M sodium nitrite was simultaneously injected

into three of the stomachs. The simultaneous production of two different nitrosamines from the same amine raises the possibility of interaction of nitrosamines; synergistic carcinogenicity, antagonistic carcinogenicity or altered organotropic action could result from such interactions.

- 6698 INDUCTION OF COLON CARCINOMAS BY 1,2-DIMETHYLHYDRAZINE HYDROCHLORIDE IN MICE. (Ger.) Thurnherr, N. (Medizinische Universitätsklinik, Kantonsspital, CH-4000 Basel, Switzerland); Reinhart, K. *Schweiz. Med. Wochenschr.* 105(18):585-586; 1975.

Weekly injections of 1,2-dimethylhydrazine-HCl (DMH, 20 mg/kg, sc) given to female NMRI mice caused focal hyperplasia and focal atypias confined to single crypts of the colon. These first histologic changes were observed as early as five weeks after the first injection. After 12 wk the number of small lesions found in serial sections of the whole colon was greater than after 36 wk. At 36 wk there were *in situ* carcinomas and carcinomas with infiltration. It appears that the focal atypias confined to single crypts may heal. With [3 H]-thymidine deoxyribose labeling a widening of the proliferative compartment was demonstrated before generalized changes were seen. After cessation of DMH exposure, these changes continue for many wk.

- 6699 ON CARCINOGENIC ACTIVITY OF 4,4'-DIAMINODIPHENYL ETHER. (Rus.) Dzhioev, F. K. (N. N. Petrov Res. Inst. Oncol. USSR Minist. Health, Leningrad). *Vopr. Onkol.* 21(3):69-73; 1975.

The potential carcinogenic effect of 4,4'-diaminodiphenyl ether (DADPE), used in the synthesis of some dyes and polymers, was studied. It was administered to 110 rats at a dose of 25 mg/1 x wk/sc or 25 mg/5 x wk/po for 1.5-9 mo and to 73 mice at 5 mg/1 x wk/sc or 5 mg/5 x wk/po for six weeks. After about two months, toxic reactions in the kidneys of both species in the form of nephrotic symptoms with a nephritic component set in involving tubules and glomeruli, and resulting in nephrosclerosis and glomerular atrophy. Adenomatous regeneration and cyst formation were seen in a number of rats. In one rat, a hypernephroid renal carcinoma was noticed. Some animals also showed fatty degeneration of the liver with simultaneous epithelial proliferation of the bile ducts. The nephrotoxic effect was more clearly defined in cases of sc administration (7 of 62 rats and 10 of 33 mice). Both modes of administration caused the same hepatotoxic effects. At the later stages of the experiment, 44% rats (7 of 16) and 57% mice (8 of 14) developed tumors in different locations (po-treated animals) and 18% rats (7 of 39) and 33% mice (3 of 9) (sc-treated animals). All observations indicated a nephrotropic effect of DADPE and a slight carcinogenic (blastomogenic) activity.

- 6700 CHANGES IN PULMONARY FUNCTION IN WORKERS EXPOSED TO VINYL CHLORIDE AND POLYVINYL CHLORIDE. (Eng.) Miller, A. (Mt. Sinai Sch. Med.,

ty Univ. New York, N.Y.); Teirstein, A. S.; Chuang, S.; Selikoff, I. J. *Ann NY Acad Sci* 246:42-52; 1975.

determine whether occupational exposure to vinyl chloride (VC) gas and polyvinyl chloride dust is associated with changes in pulmonary function, the current work force (267) plus 87 people previously employed here for more than one yr, were examined in a VC polymerization plant in Niagra Falls, New York. Clinical, occupational and smoking histories, complete physical examinations and chest roentgenograms were obtained for the entire study group. Spirometry was performed on all but six subjects. Maximum expiratory flow-vol curves for 159 workers (the first 159 subjects plus 65 selected because of abnormal spirometric findings were obtained. The clinical and roentgenographic findings will be presented separately. The major finding was diminution in air flow in 200 workers (57.5%). This abnormality was related with age and duration of exposure. For those under 40-yr-old, 53% of smokers and 28% of nonsmokers had reduced air flow ($p < 0.01$). When they exceeded 40 yr or exposure 20 yr, prevalence of air flow impairment was similar in smokers and nonsmokers, suggesting that occupational or other environmental factors were operative.

01 HUMAN, RAT AND MOUSE LIVER-MEDIATED MUTAGENICITY OF VINYL CHLORIDE IN *S. TYPHIMUR* STRAINS. (Eng.) Bartsch, H. (Int. Agency for Cancer, Lyons, France); Malaveille, C.; Montemagno, R. *Int. J. Cancer* 15(3):429-437; 1975.

The mutagenicity of vinyl chloride monomer (VCM) and its presumed metabolites in *Salmonella typhimurium* strains as mediated by tissue fractions of mouse, rat, and human origin were studied. The male BD-IV rats (100-130 g) and male OF-1 mice (30-35 g) used were fed a Charles River CRF diet. After six hours exposure to 20% VCM in air (vol/vol) strain TA 1530 was specifically reverted to His prototrophy. His mutagenic response was increased to 283% of the control value by mouse liver postmitochondrial fraction (9,000 x g supernatant); to 345% of the control for rat liver postmitochondrial fraction; and from 0-700% of the control value by four samples of this fraction from four biopsies of human livers. Phenobarbitone sodium (PB) was added to the animals' drinking water (1 mg/ml) for seven days before tissue fractionation in some experiments. This treatment increased the above mutagenic response to 457% for mouse liver fractions and to 383% for rat liver fractions. No cytotoxic effects of VCM were seen. Chloroacetic acid (a urinary metabolite of VCM) and chloroacetaldehyde were toxic, while chloroethanol was weakly mutagenic for TA 1530. The effects of subcellular fractions from mouse liver on the mutagenic response after six hours of exposure to 20% VCM at 37°C were: postmitochondrial fraction, 323% of control; microsomal fraction, 182%; cytosol supernatant after 100,000 x g 144%; and microsomal fraction plus cytosol, 522% of control. The number of His⁺ revertants minus the number of spontaneous mutations found when no tissue fraction was added was used as the control value. A causal relationship between VCM exposure and angiosarcoma of the liver in man has been established.

6702 THE IDENTIFICATION OF PHORBOLOL MYRISTATE ACETATE AS A NEW METABOLITE OF PHORBOL MYRISTATE ACETATE IN MOUSE SKIN. (Eng.) Segal, A. (New York Univ. Sch. of Medicine, New York, N.Y. 10016); Van Duuren, B. L.; Mate, U. *Cancer Res.* 35(8):2154-2159; 1975.

Phorbolol myristate acetate was identified as a metabolite of phorbol myristate acetate in mouse skin, its structure determined using spectral and chemical evidence, and its inflammatory and hyperplastic effects on mouse skin compared with those of phorbol myristate acetate. Twenty-one mice received a single application of 25 µg [³H]phorbolol myristate acetate in 0.1 ml acetone. Another group of 20 mice each received a single application of 25 µg [³H]phorbolol myristate acetate in 0.1 ml acetone. Mice were killed after five hours. The skins were removed and extracted with two 15-ml portions of methanol, acetone, ethyl ether, and chloroform, and the extracts were chromatographed. The chromatographed mouse skin extracts were applied to four thin layer chromatography plates. The amounts of phorbol myristate acetate determined per plate for the mice receiving this compound were 3.02×10^4 , 3.02×10^4 , 3.08×10^4 , and 3.15×10^4 cpm; the amounts of phorbolol myristate acetate were 646, 670, 617, and 674 cpm. Phorbol myristate acetate was not identified as a metabolite of phorbolol myristate acetate, and phorbol and phorbolol were not detected as metabolites of either compound. The comparative inflammatory effects of phorbolol myristate acetate and phorbol myristate acetate were studied by examining the degree of dermal cellular infiltration and interfollicular epidermis hyperplasia. Both phorbol myristate acetate and phorbolol myristate acetate produced considerable inflammation, with a large percentage of dermal infiltrating cells being neutrophils and a slight amount of focal sloughing of epidermis. The hyperplastic effects of phorbol myristate acetate and phorbolol myristate acetate in mouse skin were compared by counting interfollicular epidermis basal cell mitotic nuclei following metaphase arrest. The two compounds had comparable hyperplastic effects. It is concluded that phorbolol myristate acetate is the first clearly defined metabolite of phorbol myristate acetate identified in mouse skin. It is not known whether or not phorbolol myristate acetate is a tumor-promoting agent in mouse skin, or if its presence as a metabolite is related to two-stage carcinogenesis by phorbol myristate in mouse skin.

6703 RECOVERY OF A DNA-PROTEIN COMPLEX IN CULTURED MAMMALIAN CELLS FROM DAMAGE CAUSED BY 4-NITROQUINOLINE 1-OXIDE. (Eng.) Ide, T. (Inst. Medical Science, Univ. Tokyo, Shirokanedai 4-6-1, Minatoku, Tokyo, Japan); Nakane, M.; Andoh, T. *Cancer Res.* 35(11/Part 1):3146-3153; 1975.

Various metabolic inhibitors were investigated for their effects on the recovery of 4-nitroquinoline 1-oxide-damaged DNA-protein complex. Treatment of FM3A cells with 4-nitroquinoline 1-oxide caused a decrease in the sedimentation velocity of the DNA-protein complex, but did not cause a dissociation of the complex, as revealed by neutral sucrose

gradient centrifugation. Microscopic autoradiography of the complex spread on a Millipore filter demonstrated that treatment of the cells with 4-nitroquinoline 1-oxide (1×10^{-6} M, 30 min), or of the complex with Pronase E (1.5 mg/ml), gave rise to a relaxed mass of DNA fibers, in contrast to a compact mass of DNA from control cells. The damage to the DNA-protein complex was repaired completely by incubation of the cells in medium without 4-nitroquinoline 1-oxide. The following metabolic inhibitors had no effect on the repair of the complex: inhibitors of nucleic acid synthesis, α -amanitin (up to 10 μ g/ml), cordycepin (50 μ g/ml), 2-mercapto-1-(β -4-pyridethyl)benzimidazole (100 μ g/ml), 1- β -D-arabinofuranosylcytosine (1×10^{-5} M), 5-fluorodeoxyuridine (1.0 μ g/ml), and hydroxyurea (1×10^{-3} M); inhibitors of protein synthesis, cycloheximide (1 μ g/ml) and puromycin (10 μ g/ml); an inhibitor of the dark repair process in a variety of biological systems, caffeine (1 μ g/ml); inhibitors of the microtubular and microfilament system, Colcemid (0.1 μ g/ml) and cytochalasin B (3 μ g/ml), respectively; and inhibitors of energy metabolism, 2,4-dinitrophenol (30 μ g/ml), KCN (1.0 μ g/ml), iodoacetic acid (1×10^{-5} M), ouabain (1×10^{-4} M), and an atmosphere of nitrogen. Acriflavine (2.5×10^{-6} M) and actinomycin D (0.1 μ g/ml), (which are known to intercalate into DNA) caused a decrease in the sedimentation velocity of the DNA-protein complex; therefore, the effects of these agents on the recovery process remained unsolved. The repair process of the complex was, however, demonstrated to be temperature-dependent. The process was inhibited at 10 C, retarded at 28 C, but accelerated at 40 C as compared with the rate at 37 C. The finding that proteolysis and 4-nitroquinoline 1-oxide treatment gave rise to a relaxation of the DNA-protein complex suggests that the decrease in sedimentation velocity of DNA might be due to an increase in the frictional drag caused by loosening the compact conformation of the DNA-protein complex, rather than by its fragmentation, and further that 4-nitroquinoline 1-oxide induced either directly or indirectly, in the nucleus, such a conformational change of the DNA-protein complex.

- 6704 CARBON TETRACHLORIDE INDUCED POLYSOME BREAKDOWN. RELATIVE IMPORTANCE OF LIPID PEROXIDATION AND OF BINDING TO RIBOSOMAL COMPONENTS IN THE PROCESS. (Eng.) Castro, J. A. (Laboratorio de Quimica Bio-Toxicologica, CITEFA, Zafraitegui y Varela, Villa Martelli, Pcia. de Buenos Aires, Argentina); Diaz Gomez, M. I.; de Castro, C. R.; de Fenos, O. M.; de Ferreyra, E. C.; D'Acosta, N. *Res. Commun. Chem. Pathol. Pharmacol.* 10(1):93-104; 1975.

The possibility of mediation of polysome breakdown by $\cdot\text{CCl}_3$ and $\cdot\text{Cl}$ free radicals was studied. CCl_4 , CHCl_3 , or CH_2Cl_2 were given ip (20% in olive oil, 5 mg/kg) to male Sprague Dawley rats (190-260 g). In vivo, CCl_4 causes an intense polysome breakdown; the CHCl_3 effect was much less intense and the CH_2Cl_2 effect negligible. Previous administration of either diphenyl-p-phenylenediamine or α -tocopherol to the rats did not prevent CCl_4 -induced polysome breakdown. Promethazine and cystamine markedly prevented the CCl_4 induced polysome breakdown. $^{14}\text{CCl}_4$ irreversibly bound to ribosomal proteins but not to

ribosomal RNA. CCl_4 but not dimethylnitrosamine, ip, dimethylamino-azobenzene, ip, (butter yellow), thioacetamide, or tannic acid (sc) induced microsomal lipid peroxidation.

- 6705 HEAVY METAL-PYRIMIDINE NUCLEOTIDE INTERACTION: X-RAY STRUCTURE OF A CADMIUM DERIVATIVE OF CYTIDINE 5'-MONOPHOSPHATE. (Eng.) Goodgame, D. M. L. (Chemical Crystallography Inorganic Chemistry Lab., Imperial Coll., London SW7 2AY, U.K.); Jeeves, I.; Reynolds, C. D.; Skapski, A. C. *Biochem. J.* 151(2):467-468; 1975.

X-ray crystallography was used in the determination of the structure of a cadmium derivative of the pyrimidine nucleotide cytidine 5'-monophosphate [$\text{Cd}(5'\text{-CMP})(\text{H}_2\text{O})$], H_2O as part of a larger study of the sites of metal ion binding to nucleic acid components. Preliminary oscillation and Weissberg photographs showed the crystals to be orthorhombic, in the space group $\text{P}2_12_12_1$, and with cell dimensions of $a = 0.5293(1)$, $b = 1.6367(1)$, and $c = 1.7063(1)$ nm, $U = 1.4782 \text{ nm}^3$, and $Z = 4$. The structure was solved by Patterson and Fourier methods; least-squares refinement using anisotropic thermal parameters has reached $R = 0.035$. The compound has a polymeric structure in which each cadmium atom is bonded to five atoms: to the $\text{N}(3)$ position on the base, to a phosphate oxygen from each of three other 5'-CMP groups and to a water molecule. The coordination of cadmium to $\text{N}(3)$ of the cytosine ring is considered an important feature of the structure because metal binding to $\text{N}(3)$ of a cytosine unit of DNA would completely destroy its hydrogen-bonding capability to a complementary guanine. Comparison is made with a recently reported cadmium 5'-IMP compound wherein cadmium binds to ribose oxygen atoms as well as to phosphate and base. The metal atom in [$\text{Cd}(5'\text{-CMP})(\text{H}_2\text{O})$], H_2O is markedly out of the plane of the pyrimidine base. An even greater distortion of this type was observed in the Cd -5'-IMP complex. These observations suggest that because of the flexibility at the donor nitrogen atom the relative orientations of nucleic acid bases bound to a metal ion are not entirely constrained by the coordination geometry around the metal.

- 6706 POSTREPLICATION REPAIR OF ALKYLATION DAMAGE TO DNA OF MAMMALIAN CELLS IN CULTURE. (Eng.) Fujiwara, Y. (Kobe Univ. Sch. Medicine, Kusunoki-cho 7, Ikuta-ku, Kobe 650, Japan). *Cancer Res.* 35(10):2780-2789; 1975.

Differences in the repair of mouse L-cell DNA alkylated by methyl methanesulfonate (MMS) and *N*-methyl-*N*-nitrosourea (MNU) were studied. Incorporation and alkaline sucrose sedimentation studies of this DNA demonstrated the following effects of the two alkylating agents. Increasing the concentration of both agents increased the number of single-strand breaks or alkali-labile lesions of existing DNA, which reduced the incorporation of [^3H]thymidine into DNA. DNA that was newly synthesized during the first hour in [^3H]thymidine after MNU treatment was of lower molecular weight than was existing DNA with alkali-labile lesions in treated cells, and was also lower than DNA synthesized

in control cells. Such small segments formed in treated control cells. Such small segments formed in treated cells were elongated and joined to form high-molecular-weight DNA in the subsequent 4-hr chase in thymidine or 5-bromo-2'-deoxyuridine. Near UV photolysis selectively degraded 5-bromo-2'-deoxyuridine-elongated DNA to segments that are nearly as small as those before chase. Caffeine (2 mM) present during the thymidine chase prevented nascent-strand elongation, although caffeine-insensitive chain growth occurred partly in MNU-alkylated cells. The MMS lesion (single-strand breakage in alkali) in existing DNA also temporarily interrupted replicative synthesis and made short segments, but their elongation was insensitive to caffeine. The results indicate that MNU may produce both caffeine-sensitive interruptions (probably gaps), as UV damage does, and apurinic site-directed, caffeine-insensitive interruptions in nascent strands; MMS may exclusively cause the latter. Further evidence for this was the caffeine potentiation of only MNU killing, like UV killing, of L-cells. The extent of such a specific MNU lesion is estimated to be no more than 4% of the total extent of methylation, predicting that the lesion that is accessible to caffeine-sensitive repair will be a minor product(s) other than N7-methylguanine. Mutagenic and carcinogenic effects of MNU, which are higher than those of MMS, could be ascribed to such a particular MNU lesion(s) and its repair.

- 6707 A NEPHROPATHY OCCURRING IN RATS TREATED WITH DINITROCHLOROBENZENE AND N-METHYL-N¹-NITRO-N-NITROSO GUANIDINE. (Eng.) Floyd, M. (Departments Medicine, Surgery and Pathology, Univ. Newcastle upon Tyne, Newcastle upon Tyne, England); Bone, G.; Lauder, I.; Lowe, W. *Beitr. Pathol.* 155(4):343-356; 1975.

The pathological, immunological, and biochemical effects of 2,4-dinitrochlorobenzene (DNCB) with or without N-methyl-N¹-nitro-N-nitrosoguanidine (MNNG) were studied in male CFHB Wistar rats. The animals were sensitized with 10 mg DNCB in Freund's complete adjuvant injected into a hind foot pad. Some of the animals were subsequently given MNNG *ad libidum* in the drinking water (80 µg/ml) for seven months (Group M), while others were given no MNNG (Group D, controls). Both groups were given id DNCB (1 mg in benzyl alcohol) every six weeks to assess cell-mediated immunity (CMI). The urinary protein, total serum proteins, and serum lipoproteins were also measured. Kidney slices were examined histologically and for immunofluorescence to fibrinogen and immunoglobulin (Ig) G. The animals appeared healthy until weight loss was observed 9-12 mo after the beginning of the experiment. The kidneys of all treated animals, particularly those in Group M, were enlarged 2- to 3-fold and presented a finely granular surface. Urinalysis at nine months revealed a heavy proteinuria with a modest cylindruria. The mean proteinuria in the normal in the normal controls was 1.32 mg/ml; that in the Group D animals was 10.5 mg/ml; and that in the Group M animals was 13.0 mg/ml. The proteinuria was generally unselective with regard to the types of protein involved. The plasma urea,

creatinine, and electrolyte values and total serum proteins were normal, but the Group D IgG values were significantly elevated and the serum albumin levels in this group were depressed by an average of 74%. Both the Group D and Group M animals developed a severe nephropathy characterized by extensive renal cortical damage. The histological features included proliferation of the parietal epithelial cells and mesangial sclerosis; the group M rats also developed interstitial changes. Positive fluorescence for fibrinogen and IgG was observed in the more severely damaged kidneys, although IgG was more frequently observed in the Group M animals than in the Group D animals. An association between the observed nephropathy and long-term DNCB administration is suggested; this association is more likely one of direct toxicity than immune complex disease.

- 6708 A STUDY OF THE INFLUENCE OF AGE ON RESPONSE TO A CARCINOGEN. (Eng.) Roe, F. J. C. (4 Kings, Rd., London SW19, England); Peto, R.; Lee, P. N.; Clack, J. *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 157-162.

The relationship between age and response to a carcinogen, 3,4-benzpyrene (BP), was investigated in female Swiss albino mice. BP (20 µg) was applied twice weekly to the clipped dorsal skin of mice from the initial ages of 10 wk (group 1, 140 mice), 25 wk (group 2, 170 mice), 40 wk (group 3, 220 mice), or 55 wk (group 4, 420 mice). The incidence rates for epithelial tumors increased logarithmically with duration of exposure to BP; however, given duration of exposure to BP, no evidence was found of either reduced or increased susceptibility to the carcinogen with advanced age. Tumors were classified as carcinomas invading the panniculus muscle (group 1--98, group 2--115, group 3--102, and group 4--121, "probably malignant epithelial tumors" (group 1--9, group 2--8, group 3--16, and group 4--10), benign papillomas (group 1--3, group 2--5, group 3--1, and group 4--3), or sc sarcomas (group 1--1, group 2--3, group 3--10, and group 4--30). There was no evidence that age influenced the growth rate of tumors. These results suggest that the increased incidence of neoplasms with age seen in man and other animals is not due to increased susceptibility to carcinogens or to decreased efficiency of nucleic acid repair mechanisms or immunological surveillance.

- 6709 COMBINED CHEMICAL AND DNA VIRAL CARCINOGENESIS. (Eng.) Casto, B. C. (BioLabs, Inc., Northbrook, Ill.); DiPaolo, J. A. *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 122-127.

Treatment of hamster or rat embryo cells *in vitro* with chemical carcinogens enhanced transformation by

a simian adenovirus, SA7. The enhancement was linear with respect to chemical concentration and dependent upon the time of addition of chemical and virus. Interference with the metabolism of polycyclic hydrocarbons by benz(a)anthracene or 7,8-benzoflavone inhibited enhancement and cytotoxicity by benzo(a)pyrene and 7,12-dimethylbenz(a)anthracene. The inhibitory effect did not persist beyond 24 hr after treatment. All chemicals which induced single-strand DNA breaks and initiated cell DNA repair synthesis enhanced transformation by SA7. However transformation was increased by chemicals which demonstrated neither of the above properties in hamster cells. UV irradiation, or addition of any of the following, enhanced transformation by SA7: N-methyl-N'-nitro-N-nitrosoguanidine, methylmethanesulfonate, N-acetoxy-2-acetylaminofluorene, methylazoxymethanol acetate, benzo(a)pyrene, 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, dibenz(a,h)anthracene, caffeine, 5-bromodeoxycytidine, and benzo(e)pyrene. The potentiation of viral transformation by many chemical carcinogens may be due to an increased number of attachment sites for viral genomes in regions undergoing DNA repair synthesis or in sites opposite unrepaired lesions during scheduled DNA synthesis. Removal of the chemical damage prior to addition of virus may nullify the expected increase in viral transformation.

- 6710 BEHAVIORAL PARAMETERS IN RATS AND MICE BEARING TUMORS, CARCINOGENS AND INFLAMMATORY AGENTS IN THE BRAIN. (Eng.) Gershbein, L. L. (Northwest Inst. for Medical Res., 5656 West Addison St., Chicago, Ill. 60634); Benuck, I.; Shurrager, P. S. *Oncology* 31(2):103-114; 1975.

A study was conducted to elucidate the behavior of animals that had been subjected to treatment with hydrocarbons or with ascites tumor suspensions implanted into the brain. Walker tumor cells and carcinogens were implanted into the brains of male Holtzman rats, and L1210, P388, and Ehrlich ascites tumors, in addition to inflammatory agents (kaolin plus pectin or talc in saline) and hydrocarbons (3-methylcholanthrene, 9,10-dimethyl-1,2-benzanthracene, 1,2,5,6-dibenzanthracene, or azulene) were injected cortically into male BDF₁ or Swiss mice. Behavioral changes were followed in such animals by several psychological criteria; a discriminated liver-press task was given to rats, and an exploratory task (the poke test) was given to rats and mice. An activity wheel was also employed for further amplification of mouse behavior. No definite changes could be discerned by these tests between rats bearing tumor or carcinogen and the respective controls as was also the case with levels of activity in the mouse. In marked contrast, mice administered tumors or kaolin cortically demonstrated significant reductions in the mean number of pokes, especially with the higher numbers of cells injected and where neurological symptoms were evident. Behavioral changes, if any, were minimal in mice with cortically implanted carcinogens.

- 6711 THE NUCLEAR DEHYDROGENATION OF STEROIDS BY INTESTINAL BACTERIA. (Eng.) Goddard, P. (Dept. Chemistry, Liverpool Polytechnic, Liver-

pool L3 3AF, England); Fernandez, F.; West, B.; Hill, M. J.; Barnes*, P. *J. Med. Microbiol.* 8(3): 429-435; 1975.

Screening studies were done on strains of human intestinal bacteria from British and American samples of feces to determine if any of these bacteria could carry out two specific nuclear dehydrogenation (NDH) reactions. Four nuclear dehydrogenation reactions were proposed which could convert bile acids into polycyclic aromatic hydrocarbons. The strains (1,095) were tested for their ability to produce cholanyl Δ^4 -dehydrogenase and 853 strains were tested for the aromatization of 4-androsten-3,17-dione. Many strains of *Escherichia coli*, *Streptococcus faecalis*, *Bacteroides fragilis*, and others were tested. Only three strains of 100 tested of *Clostridium welchii* carried out both reactions. Also lecithinase-negative clostridia were found to carry out both reactions (about 90% of the *C. paraputrificum* strains). All strains able to aromatize 4-androsten-3,17-dione also had Δ^4 -dehydrogenase activity, but the reverse was not true. The test for a Δ^8 -dehydrogenase was not reliable, but some strains of *C. paraputrificum* (5 of 20) were able to carry out that reaction. Screening of lecithinase-negative clostridia was performed on human feces from England, Scotland, Uganda, and Hong Kong. Only a small portion of clostridia strains from Uganda (7%) and Hong Kong (12%) had NDH activity, while England (34%) and Scotland (44%) had a large proportion active. A modification of the NDH assay for Δ^4 -dehydrogenase was developed which allowed for anaerobic conditions to be used and also a shorter incubation period by the addition of 35 mg of menadione to the original reaction mixture.

- 6712 INDUCTION OF PITUITARY TUMORS IN MALE RATS BY A SINGLE DOSE OF ESTROGEN. (Eng.) Jacob, J. (Royal Brisbane Hosp., Brisbane, 4029, Australia); Lloyd*, H. M.; Meares, J. D. *Horm. Metab. Res.* 7(3):228-230; 1975.

The effect of 20 mg (sc) of diethylstilbestrol dipropionate on male rats (Sprague Dawley, 6-9 mo old) was studied. Injected and control rats were killed 406 days after the injection. The pituitary glands of 24 of the injected rats weighed 12.8 to 16.8 mg and six were over 30 mg (37-318 mg). The 24 rats with slightly enlarged glands showed no marked abnormalities in pituitary and serum prolactin and growth hormone concentrations. In the six grossly enlarged pituitary masses, prolactin concentrations were very low and growth hormone concentrations were also low. In five of these rats, serum prolactin was elevated and serum growth hormone was elevated in one. It is concluded that the grossly enlarged pituitary masses were tumors induced by the single dose of estrogen and that the moderately enlarged glands represented a state of unresolved hyperplasia.

- 6713 ENDOMETRIAL CARCINOMA IN YOUNG WOMEN TAKING ORAL CONTRACEPTIVE AGENTS. (Eng.) Silverberg, S. G. (Univ. Colorado Sch. Medicine, 4200 East Ninth St., Denver, Colo. 80220); Makowski, E. L. *Obstet. Gynecol.* 46(5):503-506; 1975.

The first 21 cases recorded in the Registry for Endometrial Carcinoma in Young Women Taking Oral Contraceptive Agents are reported. The patients were 21-39 yr old, and their conditions were histopathologically classified as adenocarcinoma, adenocanthoma, mixed adenosquamous carcinoma, clear cell carcinoma, or secretory carcinoma. No other such cases have yet been found in the literature. In 8 of the 21 patients, factors were present which militated against a close relation between oral contraceptives and carcinoma (i.e., nine patients were given contraceptives for abnormal bleeding or for ovarian histology suggestive of Stein-Leventhal Syndrome, and the others were either poorly documented or had been on the drug for less than one year). Five of these 8 patients had received only combined agents. On the other hand, 11 of the remaining 13 patients took sequential agents, a ratio directly opposite that of the usage of combined and sequential agents in the American population. In sequential agents, the mode of action involves a normal or even hyperplastic proliferative phase which is followed by shorter periods of secretion and regression; this coincides well with the data obtained, which suggest an unusually high incidence of endometrial carcinoma in women taking sequential agents.

- 6714 METABOLIC ACTIVATION OF DIETHYLSTILBESTROL: INDIRECT EVIDENCE FOR THE FORMATION OF A STILBENE OXIDE INTERMEDIATE IN HAMSTER AND RAT. (Eng.) Metzler, M. (Institut für Pharmakologie und Toxikologie der Universität, 87 Würzburg, Versbacher Landstr. 9, West Germany). *Biochem. Pharmacol.* 24(15):1449-1453; 1975.

An investigation of the *in vivo* metabolism of diethylstilbestrol in laboratory animals has led to the identification of six new metabolites from urine and bile of hamster and rat, some of which can be taken as evidence for the metabolic epoxidation of the stilbene double bond in diethylstilbestrol. Male Syrian golden hamsters and female Wistar rats were injected ip with 50 mg/kg [³H,²H]-diethylstilbestrol dissolved in 0.5 ml propane-1, 2-diol. Urine was collected in 24-hr periods for five days; bile was obtained from unanesthetized cannulated rats (10 mg/kg) and from the gall bladder of hamsters (50 mg/kg). In both rats and hamsters urinary excretion of radioactivity within five days after administration of the diethylstilbestrol was 20-30% of the dose, the radioactivity being predominantly (60-70%) associated with glucuronides. Diethylstilbestrol represented the major urinary glucuronide of the hamster but could not be detected in significant amounts in rat urine. The main glucuronide excreted by the rat was hydroxy-diethylstilbestrol. A major metabolite in both rat and hamster urine was dienestrol; two other metabolites derived from dienestrol by carrying an additional hydroxy- or methoxy-group were identified in urine. Biliary excretion of radioactivity in the rat within 18 hr accounted for 60-70% of the dose. In hamsters, the gall bladder contained 1-2% of the dose after three hours. In both species, biliary radioactivity was almost exclusively (70-80%) associated with the glucuronide fraction. Methoxy-diethylstilbestrol and dimethoxy-diethylstilbestrol were identified in the bile to-

gether with hydroxy-diethylstilbestrol and dienestrol. It is concluded that one metabolic pathway involves hydroxylation of the aromatic ring of diethylstilbestrol and methylation of one of the phenolic hydroxy-groups. A second pathway affects the stilbene double bond and leads to the formation of dienestrol and other metabolites with a hexadiene structure; this probably occurs by an epoxidation of the stilbene double bond followed by hydrolysis and loss of water from the resulting diol. The identification of metabolites with a hexadiene structure strongly supports the view that epoxidation of the stilbene double bond represents a major pathway of diethylstilbestrol metabolism. The epoxide intermediate may be related to the carcinogenic potential of diethylstilbestrol.

- 6715 FORMATION OF *N*-NITROSO COMPOUNDS: CHEMISTRY, KINETICS, AND *IN VIVO* OCCURRENCE. (Eng.) Mirvish, S. S. (Univ. Nebraska Med. Cent., Omaha). *Toxicol. Appl. Pharmacol.* 31(3):325-251; 1975.

The chemistry and kinetics of *in vitro* and *in vivo* nitrosation, including that of drugs, pesticides, and food preservatives are reviewed. A discussion of the chemistry of *N*-nitroso compound (NO-compounds) formation reveals the potent carcinogenicity of most tested nitrosamines and nitrosamides. The preparation of NO-compound derivatives and C-nitroso compounds are also discussed; the latter are either noncarcinogenic, or weaker carcinogens than NO-compounds. The results of kinetic studies, generally followed by the UV absorption of the NO-compounds, show that *N*-alkylurea, *N*-arylsurea, *N*-alkylcarbamates, secondary aromatic amines, secondary amine derivatives of piperazine and morpholine, and tertiary enamines are more readily nitrosated than simple aliphatic secondary and tertiary amines (*N*-acylureas, and *N*-alkylguanidines). The kinetics are modified by catalysts; however, the ease of nitrosation generally increases as the basicity of the amines (i.e. pKa) decreases. Long term experiments on *in vivo* nitrosation, involving the induction of tumors by oral administration of amines or amides together with (+) nitrate, are reviewed. Acute experiments involving liver necrosis and intragastric nitrosation, nitrosation in hypoaacidic stomachs, the large intestine, the infected urinary bladder, the infected vagina, and nitrosation by bacteria are discussed. A high incidence of gastric cancer is correlated with high nitrate content of drinking water, and/or use of nitrate fertilizer. The effect of ascorbate and other compounds reacting with nitrite is discussed. Further mention is given to nitrosation of drugs and pesticides, many of which are nitrosated under extreme conditions, yet give only minute yields of NO-compounds under milder conditions. Several chemical studies that could be performed on each of 41 drugs and pesticides, and on 22 naturally occurring compounds, all of which form NO compounds, are presented as methods of evaluating the hazard of exposure.

- 6716 COLLAGEN, GLYCOSAMINOGLYCANS AND HISTAMINE IN LUNGS OF GUINEA PIGS EXPOSED CHRONICALLY TO CIGARETTE SMOKE. (Eng.) Dabrowski, R. (Inst. Pathol., Med. Acad., Lodz, Poland); Maś-

liński, C. *Bull. Acad. Pol. Sci. [Biol.]* 23(2):125-128; 1975.

The chronic effects of cigarette smoke on the level of total collagen, its soluble fractions, and glycosaminoglycans were investigated in guinea pig lungs. The concentration of histamine in the blood was determined at various times during the experiment and in the lungs at the end of the experimental period. The guinea pigs were exposed to smoke 15 min daily for the first six days and then for 30 min daily for 190 days. At 4, 8, 12 and 28 wk, blood was taken during a smoking session. After 196 days, experimental and control animals were killed, and the lung tissue was taken for determination of collagen, glycosaminoglycans, and histamine. Total collagen and its soluble fraction were determined in 0.15 M NaCl (pH 7.2), and also in citrate buffer, pH 3.8. The level of collagen was determined by measuring the amount of hydroxyproline. Glycosaminoglycans were determined in the individual fractions following separation of CF-11 columns. The histamine level in blood was significantly higher in the smoked animals between weeks 8-12 of smoking than in the controls. After 28 wk of smoking, however, the histamine level in the blood of the experimental animals was still higher, but not significantly so. The total collagen content (and both its soluble fractions) was considerably higher in the lungs of the smoked (55.44 mg/100 g fresh tissue) than of the control (29.26 mg/100 g fresh tissue) animals. Glycosaminoglycans were considerably lower in the smoked animals (12.00 µg as uronic acids/100 mg dry tissue) than in the controls (19.57 µg/100 mg dry tissue). After separating the glycosaminoglycans on CF-11 columns, the levels of hyaluronic acid, chondroitin sulfates, and heparin were significantly lower in the lungs of the smoked animals. It is concluded that cigarette smoke causes considerable changes in the connective tissue of the lungs as indicated by the increase in collagen synthesis, accounting for the higher level of both total collagen and its soluble fractions as well as for the decrease in the glycosaminoglycans and histamine.

6717 CILIARY ALTERATIONS IN HAMSTER RESPIRATORY TRACT EPITHELIUM AFTER EXPOSURE TO CARCINOGENS AND CIGARETTE SMOKE. (Eng.) Reznik-Schuller, H. (Abteilung fuer Experimentelle Pathologie, Medizinische Hochschule Hannover, 3000 Hannover-Kleefeld, Karl-Wiechert-Allee 9, West Germany). *Cancer Lett.* 1(1):7-13; 1975.

The cilia of the respiratory epithelium of Syrian golden hamsters was examined for abnormalities after exposure to cigarette smoke and during the development of respiratory tract tumors induced by known carcinogens. Benzo(a)pyrene (BP, 0.63 mg/animal) was intratracheally administered once weekly for life to one group of hamsters and the sequential alterations of the respiratory epithelium were examined during the first 20 wk treatment. A second group was exposed to the total smoke of 30 unfiltered research cigarettes by means of a smoking machine once daily for 7 yr. A group of European hamsters (strain MHH:EPH) was treated sc once weekly for life with 1/40 the N-dibutyl-

nitrosamine (DBN) LD₅₀ (61.1 mg/kg of body weight for males; 46.7 mg/kg for females). Specimens were taken from the trachea, lobar and segmental bronchi. From the DBN-treated animals, parts of macroscopically visible pulmonary tumors were examined. In all three animal groups, ciliary abnormalities were observed, occurring in the trachea, lobar and segmental bronchi of BP-treated and smoke-exposed animals, and in the bronchi from which adenocarcinoma originated in the DBN-treated animals. The abnormalities consisted of cytoplasmic surface projections of various sizes and shapes in the DBN-treated animals. Intracellular cilia were only found in the epithelia of BP-treated animals. The formation of these abnormalities seemed to represent a nonspecific response of the epithelium to the carcinogen treatment that is independent of the developing tumor type. Nevertheless, they indicated a disturbance in the cellular concept for the formation of cilia, causing damage of the normal ciliary defense mechanism against noxious agents. This would increase the susceptibility of the entire epithelium to subsequently encountered noxious agents and thereby increase the cancer risk.

6718 HISTOPATHOLOGICAL STUDIES OF THE NERVOUS SYSTEM TUMORS IN RATS INDUCED BY N-NITROSO-METHYL-UREA. (Eng.) Ishida, Y. (Gunma Univ. Sch. Medicine, 3-39-22 Showa-machi, 371 Maebashi-shi, Gunma-ken, Japan); Tamura, M.; Kanda, H.; Okamoto, K. *Acta Pathol. Jpn.* 25(4):385-401; 1975.

Histological characteristics of N-nitroso-methyl-urea (NMU)-induced tumors of the peripheral nervous system were studied in the Donryu rat. The rats were given weekly injections of 5 or 10 mg/kg NMU or a single administration of 50 mg/kg NMU through the mothers. A total of 176 neural and nonneural neoplasms were produced. Of the tumors produced, those of the peripheral nervous system amounted to 121, comprising 68.7% of the total number of the neoplasm. Microscopically, most of the nerve tumors showed histological characteristics corresponding to those of human neurinomas. Many tumors, however, disclosed anaplastic cytological appearance. Fifteen gliomas were produced in the brain and spinal cord. They were classified as mixed glioma, oligodendroglioma and anaplastic astrocytoma. The commonest brain tumors produced in rats from the iv treated group were periventricular mixed gliomas, while gliomas in rats from transplantally treated group showed an isomorphic histology with a close resemblance to that of oligodendroglioma.

6719 THE EFFECT OF HEAVY METAL IONS ON THE RATE OF DECOMPOSITION OF N-ETHYL-N-NITROSOUREA AND OTHER CARCINOGENIC N-NITROSAMIDES. (Eng.) Preussmann, R. (Deutsches Krebsforschungszentrum, Institut für Toxikologie und Chemotherapie, D-6900 Heidelberg, Im Neuenheimer Feld 280, West Germany); Deutsch-Wenzel, R.; Eisenbrand, G. *Z. Krebsforsch.* 84(1):75-80; 1975.

The decomposition kinetics of N-nitrosamides in aqueous solution in the presence of heavy metal salts were studied. N-ethyl-N-nitrosourea (ENU, 2×10^{-5}

M/1), *N*-methyl-*N'*-nitro-nitrosoquandine (MNNG), or *N*-methyl-*N*-nitrosourethane were dissolved in 0.9% saline at 37 C in the presence of CuSO_4 , NiSO_4 , CoSO_4 , ZnSO_4 , MnSO_4 , or FeSO_4 (each 1×10^{-5} M/1). The decomposition of ENU in this solution was enhanced by Cu^{2+} and, to a lesser extent, Ni^{2+} . The decomposition of MNNG was also strongly enhanced by Cu^{2+} and, to a lesser extent, Ni^{2+} . In contrast, the stability of *N*-methyl-*N*-nitrosourethane was not influenced by heavy metal ions. The influence of Cu^{2+} ions on the decomposition of ENU was similar to that of OH^- , influencing the reaction kinetics on a molar basis. The increase in the decomposition rate of ENU by Cu^{2+} was not seen in the presence of blood serum or other complexing agents, and none of the other heavy metal ions enhanced the decomposition of ENU in aqueous solution. The fact that nickel, copper, cobalt, iron, and manganese sulfates have all been known previously to raise the local carcinogenic action of ENU indicates that the heavy metal salts *in vivo* do not act exclusively by accelerating nitrosamide degradation.

6720 SUBSTRATES AND INHIBITORS OF HEPATIC GLUTATHIONE-S-EPOXIDE TRANSFERASE. (Eng.)

Hayakawa, T. (Roche Inst. Molecular Biology, Nutley, N.J. 07110); Udenfriend*, S.; Yagi, H.; Jerina, D. M. *Arch. Biochem. Biophys.* 170(2):438-451; 1975.

The substrate specificity of glutathione-S-epoxide transferase and the effects of some inhibitors of this enzyme were investigated in the 100,000g supernatant from sheep liver and in a purified preparation from the same source. Most of the assays for transferase activity were based on a sensitive radioisotope procedure developed to measure conjugate formation between naphthalene 1,2-oxide and [^{35}S]glutathione by replacing the naphthalene oxide with other compounds. Products formed in incubation mixtures containing [^{35}S]glutathione (4×10^5 to 5×10^5 cpm/ $0.5 \mu\text{M}$), substrate, and enzyme were analyzed radio-metrically after paper chromatography. When radio-active oxides were used as substrates with nonradio-active glutathione ($5 \mu\text{M}$), incubation mixtures included [$2\text{-}^3\text{H}$]naphthalene 1,2-oxide (3×10^5 cpm/ $0.5 \mu\text{M}$) or [$7\text{-}^3\text{H}$]styrene oxide (4×10^5 to 5×10^5 cpm/ $1.2 \mu\text{M}$). Purification factors of 30- to 60-fold were observed for nearly 50 simple epoxides and arene oxides. The similarity in purification factors suggests either that a single enzyme with activity toward simple epoxides and arene oxides was purified, or that several related enzymes were copurified. Comparisons of specific activities for benzene oxides, naphthalene oxide, phenanthrene oxide, and arene oxides of benzo[a]pyrene and dimethylbenzanthracene established that (1) benzene oxides are poor substrates unless strong electron withdrawing substituents are present; (2) naphthalene oxide is a good substrate; and (3) increasing the size of polycyclic arene oxides causes a steady decrease in activity. Reactivity toward simple epoxides was compared with that for epoxide hydrazase. The transferase was not readily inhibited by any of the compounds used, and showed a strict requirement for glutathione. It is emphasized that rates of both enzymatic and nonenzymatic conjugation of the arene oxides of polycyclic hydrocarbons steadily decreased as the

size of the ring systems increased. Thus, a protective role for glutathione against polycyclic hydrocarbon-induced carcinogenesis *via* arene oxides is not evident.

6721 EPOXIDE HYDRAZE ACTIVITY IN MOUSE SKIN EPIDERMIS. (Eng.) Pyerin, W. G. (Deutsches

Krebsforschungszentrum Institut für Biochemie D-6900 Heidelberg 1, Federal Republic of Germany in Neuenheimer Feld 280); Hecker, E. *Z. Krebsforsch.* 83(1):81-83; 1975.

Mouse epidermis homogenates were fractionated to enrich epoxide hydrazase activity up to a range of specific activity which would permit the application of the radiometric styrene epoxide method for determining enzyme activity. Scraping of the epidermal layer of shaved areas of NMRI female mice were homogenized in 0.25 M sucrose solution. The homogenate was centrifuged twice at $8,500 \times g$ for 10-15 min. The supernatant was centrifuged at $105,000 \times g$ for 90 min to pellet a microsomal fraction. Epoxide hydrazase activity was measured using $7\text{-}^3\text{H}$ -styrene oxide as substrate. After removal of unreacted substrate by extraction with petroleum ether, the glycol was extracted into ethyl acetate for assay by scintillation spectrometry. In experiments designed to establish the optimal conditions for the assay, the following results were obtained: (1) product formation was linear with time up to 25-30 min at pH 9.0 and 37 C, (2) product formation was linear with protein concentration using up to about 700 μg protein/flask at pH 9.0, 37 C in 25-min incubations, (3) buffer TRIS-HCl, pH 9.0 concentrations of 100-200 mM did not influence product formation at 37 C for 25 min, and (4) optimum pH was 8-9. The specific epoxide hydrazase activities and the distribution of the epoxide hydrazase activity in the different fractions of the mouse epidermis homogenate are tabulated.

6722 THE EFFECT OF AF2 [2-(2-FURYL)-3-(5-NITRO-2-FURYL)ACRYLAMIDE] ON HEPATIC MICROSOMAL MIXED FUNCTION OXIDASE SYSTEM IN RATS. (Eng.)

Fukuhara, M. (Inst. Public Health, 6-1, Shirokanedai 4 chome, Minato-ku, Tokyo, 108, Japan); Takabatake, E. *Chem. Pharm. Bull. (Tokyo)* 23(7):1626-1628; 1975.

6723 ALCOHOLISM IN CANCER OF THE HEAD AND NECK. (Eng.) Lowry, W. S. (Dept. of Cancer

Studies, The Queen's Univ. of Belfast, Ireland). *Laryngoscope* 85(8):1275-1280; 1975.

6724 DESTRUCTION OF TRIPLET NITRENIUM ION BY ASCORBIC ACID. (Eng.) Scribner, J. D.

(Fred Hutchinson Cancer Res. Cent., Seattle, Wash.); Naimy, N. K. *Experientia* 31(4):470-471; 1975.

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- 6801 PEROXIDATED LIPID CONTENT OF HUMAN BREAST FLUID [abstract]. (Eng.) Petrakis, N. L. (G. W. Hooper Found., Univ. California, San Francisco); Doherty, M. A.; Lee, R. E.; Beelen, G. *Proc. Am. Assoc. Cancer Res.* 16:157; 1975.
- 6802 INHERENT SPECIFICITIES OF PURIFIED CYTOCHROMES P-450 AND P-448 TOWARD BIPHENYL HYDROXYLATION AND ETHOXYRESORUFIN DEETHYLATION. (Eng.) Burke, M. D. (Dept. of Forensic Medicine, Karolinska Institutet, S-104 01, Stockholm 60, Sweden); Mayer, R. T. *Drug Metab. Dispos.* 3(4):245-253; 1975.
- 6803 INTERACTION OF AROMATIC NITRO COMPOUNDS WITH REDUCED HEPATIC MICROSOMAL CYTOCHROME P-450. (Eng.) Sternson, L. A. (McCollum Lab, Campus West, Univ. of Kansas, Lawrence, Kans. 66044); Gammans, R. E. *Drug Metab. Dispos.* 3(4):266-274; 1975.
- See also:
- * (Rev): 6601, 6602, 6603, 6604, 6605, 6606, 6607, 6608, 6609, 6610, 6624, 6627, 6631, 6641, 6643, 6644, 6645, 6646, 6654, 6655, 6663
 - * (Phys): 6810, 6815, 6821, 6823, 6825, 6828
 - * (Immun): 6929, 6981
 - * (Path): 7017, 7018, 7020, 7041, 7043, 7045, 7050, 7071, 7098
 - * (Epid-Biom): 7114, 7115, 7116, 7127, 7128, 7129, 7130, 7131, 7132, 7133, 7134, 7140, 7141, 7142, 7143, 7150

PHYSICAL CARCINOGENESIS

- 6804 X-RAY-INDUCED CHROMOSOME ABERRATIONS IN OOCYTES OF MICE. II. SENSITIVE STAGES IN THE OOGENESIS. (Eng.) Hansmann, I. (Institut für Humangenetik, Universität Göttingen, Nikolausbergerweg 5a, West Germany); Reichert, W.; Röhrborn, G. *Mutat. Res.* 29(2):218; 1975.

The effects of X-irradiation on chromosome aberrations in different stages of meiosis were studied in female NMRI mice. The animals were treated at 10-12-wk of age with 1.5 IU pregnant mare's serum (PMS) and 2.0 IU human chorionic gonadotrophin (HCG) for stimulated ovulation. After ovulation at the stage of metaphase II, the chromosomes were analyzed for numerical and structural anomalies. Prenatally, the mice were exposed to 22.2 R on the eleventh, thirteenth, or seventeenth day of gestation; postnatally, 1-, 3-, and 6-wk-old mice were exposed to 66.6 R or 22.2 R (3-wk-old mice only). None of the females that had been treated at one week of age ovulated, and only 17% of those treated at three weeks ovulated. The number of ovulated oocytes per female in the latter group decreased to 4.4 as compared with 8.9 in the nonirradiated controls. A significant increase in structural chromosomal anomalies was observed only in the oocytes from females irradiated at six weeks. The sensitivity for X-ray-induced structural anomalies decreased from the preovulatory phase to the di-cytotene in six weeks, and to 3-wk-old females in whom no increase over the control frequency was observed. A slight but nonsignificant increase in structural anomalies was observed after prenatal irradiation. In addition, diploid oocytes were observed in mice irradiated on the 11th or 13th day of gestation.

- 6805 THE EFFECT OF A 24-HOUR FRACTIONATION INTERVAL ON THE INDUCTION OF RAT SKIN TUMORS BY ELECTRON RADIATION. (Eng.) Burns, F. J. (Inst. Environ. Med., New York Univ. Med. Cent., N.Y.); Albert, R. E.; Sinclair, I. P.; Vanderlaan, M. *Radiat. Res.* 62(3):478-487; 1975.

Tumor incidence and hair follicle lethality in male CD rat skin were determined after various single and split doses of monoenergetic electrons produced by a Van de Graaff accelerator. In the split-dose groups, an initial dose of 1000 rads was followed 24 hr later by graded doses from 1000 rads to 4000 rads. The cumulative number of tumors per rat increased steadily in all groups consistent with a linear dependence on time after a somewhat variable tumor-free period. Hair-follicle survival was determined at death of the animal, and dose displacement of the response curves was equivalent to about 80% of the initial dose. The curve of tumor response at 70 wk *versus* dose was peaked, but the ascending limbs of the curves were displaced by at least 70% of the initial dose. Kinetic study of mammalian cells in culture indicates that about 50% recovery occurs within 2-4 hr after the initial dose when recovery is of the intracellular type. Therefore it was concluded that oncogenic recovery was too rapid for cell repopulation to be significantly involved and that most, if not all, of the

observed recovery was based on a relatively rapid process of the intracellular type.

- 6806 CONTINUING OCCURRENCE OF THYROID CARCINOMA AFTER IRRADIATION TO THE NECK IN INFANCY AND CHILDHOOD. (Eng.) Refetoff, S. (Thyroid Stud. Unit, Univ. Chicago, Ill.); Harrison, J.; Karanfilski, B. T.; Kaplan, E. L.; De Groot, J.; Bekerman, C. *N. Engl. J. Med.* 292(4):171-175; 1975.

Patients (47 men and 53 women) who voluntarily sought medical attention because of a knowledge of prior irradiation and its possible link with thyroid cancer were examined. Irradiation had been given to tonsils (42%), adenoids (10%), tonsils and adenoids (7%), and thymus (30%), for acne (7%) and for other reasons (7%). The age at irradiation ranged from 4.4 to 4.8 yrs. Patients were examined on two consecutive visits, spaced one or several weeks apart, and were subjected to physical examination and a battery of diagnostic tests. Operation was recommended for 18/26 patients with palpable abnormalities and 15 were operated upon; 7/15 had carcinomas and the rest had benign lesions. Among the patients with carcinoma, two had a single nodule on palpation, four had multinodular glands, and one had a diffusely enlarged gland with a granular surface. There was one papillary, four mixed papillary-follicular and two follicular carcinomas. Of seven patients irradiated to both tonsils and adenoids, thus receiving greater radiation exposure, two had carcinoma, suggesting a dose relation. The overall 7% prevalence of carcinoma in unselected patients with a history of irradiation to the neck area is higher than expected and indicates that radiation-associated thyroid carcinoma has not disappeared, although at least 15 yr have elapsed since irradiation for benign conditions of childhood and infancy was common practice.

- 6807 RADIATION CARCINOGENESIS. (Eng.) Son, Y. H. (Yale Univ. Sch. Medicine, 789 Howard Ave., New Haven, Conn. 06510). *Cancer* 36(3):941-945; 1975.

Two cases of tumors strongly suspected to be radiation-induced are reported. A 48-yr-old man received X-ray therapy of indeterminable quantity to the skin of the back of the neck and shoulder for a severe case of acne at age 16. Thirty-two years later, a nodule was discovered on the right lobe of the thyroid. Right lobectomy showed Hurthle cell adenoma and multifocal papillary adenocarcinoma. A 68-yr-old man received 4,350 R in 17 days for Grade I squamous cell carcinoma of the nasopharynx in 1948. Eight years later, he developed a marble-sized mass in the lower pole of the right parotid gland, which was apparently included in the radiation field. Right parotidectomy revealed mucoepidermoid carcinoma. Radiation is known to induce a spectrum of histologic changes in the thyroid ranging from adenoma to papillary adenocarcinoma. Salivary glandular tumor is also a recognized entity among radiation-induced tumors.

- 6808 THE LONG-TERM EFFECTS OF INTRATRACHEALLY INSTILLED $^{253}\text{EsCl}_3$ IN RATS. (Eng.) Bal-lou, J. E. (Pacific Northwest Lab., Richland, Wash.); Dagle, G. E.; Morrow, W. G. *Health Phys.* 29(2):267-272; 1975.

The effects of radiation dose rate and dose distribution on the induction of latent effects such as lung and bone tumors were studied in SPF Wistar rats of both sexes. $^{253}\text{EsCl}_3$ was administered intratracheally at 0.214, 10.7, 47.2, and 2.5 $\mu\text{Ci/kg}$; controls were given the 0.01 N HCl (pH 2) vehicle alone. The animals were observed for up to 880 days after treatment. In females given 2.5 $\mu\text{Ci/kg}$, the lung and skeleton were the major repositories of radioactivity, although other soft tissues accounted for as much as 15-20% of the retained radionuclide. Clearance from the lung could be described as the sum of two exponential functions having effective half-lives of 1 and 9 days, respectively. The ^{253}Es in the skeleton increased over the 42-day observation period and appeared to be cleared by radioactive decay only; clearance from other tissues appeared to fit single exponential functions. In males given 0.214-47.2 $\mu\text{Ci/kg}$, the lung accumulated 8-fold more radioactivity than did the skeleton. About 13% of the cumulated lung dose was associated with the fraction cleared, with a half-life of 1.2 days. The first obvious effect of ^{253}Es incorporation in the males was a dose-dependent depression in weight gain. Median survival time was also decreased in a dose-dependent fashion. Neither weight nor survival were affected by the 0.21 $\mu\text{Ci/kg}$ dose. The most common lesion and major cause of death in the 47.2 $\mu\text{Ci/kg}$ group was radiation pneumonitis, although two animals developed tumors (an osteosarcoma and a benign tumor of the adrenal cortex). Rats in the 10.7 $\mu\text{Ci/kg}$ group died primarily as a result of tumor growth and metastasis; 42% of the rats developed bone tumors and 33% developed malignant tumors of soft-tissue origin and/or leukemia. Benign or malignant tumors were found in 92% of these animals. Rats in the 0.21 $\mu\text{Ci/kg}$ group developed nearly the same number of bone tumors as those in the 10.7 $\mu\text{Ci/kg}$ group, but were free of bone tumors. Controls given the HCl vehicle developed soft tissue tumors and leukemia, but had no tumors of the kidney, lung, or skeleton. The data indicate that ^{253}Es was the causative agent in the induction of malignancies in the kidney, lung, and skeleton, and they support the view that alpha-induced radiation damage is irreparable.

- 6809 NEOPLASIAS AMONG THE ATOMIC BOMB SURVIVORS IN JAPAN. (Eng.) Watanabe, S. *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 114-119.

The incidence of neoplasms among the atom bomb survivors of Hiroshima and Nagasaki is discussed including leukemia, malignant lymphomas, carcinoma of the thyroid, lung, stomach, breast, ovary, and uterus, and tumors of the salivary glands. From 1946 to 1972, 270 leukemia cases were recorded for

the exposed population in Hiroshima, of whom 208 were within 2000 m from the hypocenter. Sixty-seven cases of leukemia were found among the survivors in Nagasaki between 1945-1959. The 208 cases of leukemia among Hiroshima survivors who were exposed within 2000 m were divided into two groups according to onset time: 148 cases (71.2%) were observed within 15 yr (1946-1960) after exposure, and only 60 cases in the 12 yr period 1961-1972. The relationship between the incidence of leukemia type in Hiroshima and Nagasaki and the intensity of the exposure evaluated by distance from the hypocenter was investigated; the incidence of both acute and chronic leukemia among the survivors exposed within 1000 m from the hypocenter was higher in Hiroshima than in Nagasaki. The results also suggested that the prevalence of chronic granulocytic leukemia in Hiroshima may have resulted from the more intensive radioactivity of the neutron components of the bomb in Hiroshima than in Nagasaki. The first case of thyroid carcinoma among the survivors in Hiroshima was detected five years after exposure with the highest incidence seen 16-20 yr later. Comparisons of data on the incidence of carcinoma of the lung in Hiroshima and Nagasaki indicate that the rate of carcinoma of the lung was higher in Nagasaki than in Hiroshima. On the other hand, gastric carcinoma was more prevalent in Hiroshima than in Nagasaki. The incidence of carcinoma of the breast increased significantly among the exposed females in Hiroshima and in the heavily exposed group (100 rad and over) ranged from two to several times higher than that in the control groups. An increase in breast carcinoma among survivors of Nagasaki could not be confirmed in at least two studies. There was a significant increase of carcinoma of the ovary but not of the uterus among the heavily irradiated survivors of both cities. A significant increase in malignant salivary gland tumors has been seen in survivors from Hiroshima since 1957. It is concluded that comparative studies of the survivors of Hiroshima (which received much greater amounts of neutron irradiation) and Nagasaki would be useful in classifying the carcinogenic effects of neutrons.

- 6810 THE INHIBITORY EFFECT OF CAFFEINE ON THE INDUCTION OF CUTANEOUS TUMORS IN MICE BY ULTRAVIOLET RAYS. (Eng.) Zajdela, F. (*Unité de Physiologie Cellulaire de l'I.N.S.E.R.M., Bt. 110, Institut du Radium, 91405 Orsay, France*); Latarjet, R. *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 120-124.

Female S.P.F. mice (nonhomozygous Swiss strain) were exposed to the total radiation of a mercury vapor lamp under conditions such that tumors developed on the ears of 90% of the controls in 1 yr. The animals' right ears were painted with a caffeine solution (40 mm³ of 0.2% caffeine in acetone-chloroform) and their left ears were painted with the solvent alone. Tumor incidence was about 90% in the left ears and only 50% in the right ears. Inhibition of tumorigenesis was similar with theo-

- phylline. Tumor incidence did not diminish when uridine was used to test the effect of a UV-absorbant substance. Most of the tumors were accompanied by cervical metastases; 90% of the tumors were keratogenic epitheliomas and 10% were sarcomas of subepidermic origin. Autoradiography with tritium-labeled caffeine showed that caffeine in acetonetic solution passes easily into the epidermic tissue. These results suggest that carcinogenesis by UV rays is triggered by a DNA repair mechanism that, while permitting the cells to survive, leaves a "particular error" in the DNA and even favors its production.
- 6811 CARCINOGENIC EFFECT ON THE CHRYSOTILE-ASBESTOS DUST IN EXPERIMENTS. (Rus.) Kogan, F. M. (Inst. Industrial Hygiene and Occupational Diseases, Sverdlovsk, U.S.S.R.); Morozova, K. I.; Pylev, L. N. *Gig. Tr. Prof. Zabol.* (6):31-35; 1975.
- 6812 THE DETERMINATION OF ^{210}Po IN URINE. (Eng.) Bale, W. F. (Univ. Rochester, Sch. Medicine Dentistry, Rochester, N.Y. 14642); Helmkamp, R. W.; Hrynyszyn, V.; Contreras, M. A. *Health Phys.* 29(5):663-671; 1975.
- 6813 ACTION OF STRONTIUM-90 CHRONICALLY ADMINISTERED TO RATS ON CERTAIN PARTS OF THEIR DIGESTIVE CANAL. (Rus.) Boitsova, V. P. (No affiliation given); Goloshchapov, P. V.; Soroka, L. P. *Radiobiologiya* 15(3):389-393; 1975.
- 6814 DEPENDENCY OF THE AVERAGE LIFE, MORTALITY AND OSTEOSARCOMA OCCURRENCE IN RATS ON THE RADIATION DOSE ABSORBED (Sr^{90}). (Rus.) Shvedov, V. L. (No affiliation given); Panteleev, L. I. *Radiobiologiya* 15(3):402-406; 1975.
- 6815 CALCULATION OF EXTERNAL IRRADIATION IN A URANIUM MINE. (Fre.) Fourcade-Cancelle, N. (Commissariat a l'Energie atomique, Departement de Protection, B.P. n° 6, 92260 Fontenay-aux-Roses, France). *Radioprotection* 10(1):11-28; 1975.
- 6816 COMPARISON OF THREE METHODS FOR THE DIRECT MEASUREMENT OF HIGH RADON CONCENTRATIONS IN THE AIR. (Fre.) Renoux, A. (Laboratoire de Physique Aerosols et Radioactive atmospherique, Faculte Sciences Brest, U.B.O., avenue Victor-Le-Gorgue, 29200 Brest, France); Mouden, A.; Madelaine, G. *Radioprotection* 10(1):29-40; 1975.
- 6817 INACTIVITY OF 5-HYDROXYTRYPTOPHAN AGAINST THE DEPRESSION OF THE ANTITUMOR ACTIVITY OF THE HOST ANIMAL AS INDUCED BY WHOLE BODY X-RAY IRRADIATION. (Fre.) Nakamura, W. (Res. Inst., Aichi Cancer Center, Nagoya, Japan); Nishimoto, Y. *C. R. Soc. Biol. (Paris)* 169(2):468-472; 1975.
- 6818 CYTOGENETIC EXAMINATION OF THE SIX-YEAR IRRADIATED DOGS. (Rus.) Tsessarskaia, T. P. (No affiliation given). *Radiobiologiya* 15(3):434-437; 1975.
- 6819 IRRADIATION-INDUCED ADDUCT FORMATION OF RNA WITH CARCINOGENIC ARYLAMINE DERIVATIVES. (Eng.) Cardona, R. A. (Michael Reese Hosp. and Medical Center, Chicago, Ill. 60616); King*, C. M.; Redpath, J. L. *Cancer Res.* 35(8):2007-2014; 1975.
- 6820 DNA REPAIR SYNTHESIS DEPENDENT ON THE *wvrA,B* GENE PRODUCTS IN TOLUENE-TREATED CELLS. (Eng.) Moses, R. E. (Baylor Coll. Medicine, Houston, Tex. 77025); Moody, E. E. M. *J. Biol. Chem.* 250(20):8055-8061; 1975.
- 6821 FILM CARCINOGENESIS. (Eng.) Autian, J. (Center Health Sciences, Univ. Tennessee, Memphis, Tenn.). *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 94-101.
- 6822 ADRENAL "A" CELL PROLIFERATION AS A RADIATION RESPONSE. (Eng.) Gates, O. (N. Engl. Deaconess Hosp., Boston, Mass.); Warren, S. *Fed. Proc.* 34(3):825; 1975.
- 6823 A RADIATION-INDUCED CELL CYCLE MARKER FOR CYCLOHEXIMIDE SENSITIVITY [abstract]. (Eng.) Brewer, E. N. (Dep. Radiology, Case Western Reserve Univ., Cleveland, Ohio 44106); Oleinick, N. L.; Rustad, R. C. *Radiat. Res.* 62(3):536; 1975.
- 6824 A PRACTICAL CALCULATION METHOD OF THE DISTRIBUTION FUNCTION OF THE RISK BY IRRADIATION. (Eng.) Wolber, G. (EdF-France). *Trans. Am. Nucl. Soc.* New Orleans, Louisiana, June 9-13, 1975. Edited by Farmakes, R. Hinsdale, Ill., American Nuclear Society, Inc., 1975, p. 87.
- 6825 THE TUMORIGENIC EFFECTS OF PSORALEN AND ULTRAVIOLET LIGHT [abstract]. (Eng.) Grube, D. D. (Div. Biol. Med. Res., Argonne Natl. Lab., Ill.); Ley, R. D.; Fry, R. J. M. *Proc. Am. Assoc. Cancer Res.* 16:117; 1975.
- 6826 COMPARATIVE SURVIVAL OF LETHALLY IRRADIATED INBRED MALE MICE INOCULATED WITH MARROW FROM VIRGIN OR MULTIPAROUS FEMALE DONORS. (Eng.) Uphoff, D. E. (Natl. Cancer Inst., Bethesda, Md. 20014). *J. Natl. Cancer Inst.* 54(6):1343-1348; 1975.

6827 ON THE FATE OF STABLE CHROMOSOMAL ABERRATIONS. (Eng.) Carrano, A. V. (Biomedical Div., Lawrence Livermore Lab., Livermore, Calif. 94550); Minkler, J.; Piluso, D. *Mutat. Res.* 30(1):153-156; 1975.

6828 SYNERGISTIC CARCINOGENIC EFFECT OF PRO-CARBAZINE AND IONIZING RADIATION IN CDF MICE [abstract]. (Eng.) Arseneau, J. C. (Univ. Rochester, N.Y.); Fowler, E.; Bakemier, R. F. *Proc. Am. Assoc. Cancer Res.* 16:120; 1975.

See also:

- * (Rev): 6606, 6611, 6612, 6613, 6614, 6631, 6647, 6648, 6649, 6650, 6651, 6652, 6653
- * (Chem): 6732, 6775
- * (Viral): 6870
- * (Epid-Biom): 7124, 7125, 7126

VIRAL CARCINOGENESIS

- 6829 ONCOGENIC TRANSFORMATION OF MURINE LYMPHOID CELLS BY *IN VITRO* INFECTION WITH ABELSON LEUKEMIA VIRUS. (Eng.) Raschke, W. C. (Salk Inst. Biological Studies, P.O. Box 1809, San Diego, Calif. 92112); Ralph, P.; Watson, J.; Sklar, M.; Coon, H. *J. Natl. Cancer Inst.* 54(5): 1249-1253; 1975.

An *in vitro* system was used for the study of early events in the transformation of lymphoid cells by a C-type RNA virus. Six-wk-old female BALB/c mice were immunized iv with 0.2 ml of 10% sheep RBC; after three days, spleens were harvested and cultured. The cultures were infected with either Moloney virus or an Abelson virus pool and contained either 3×10^6 sheep RBC, 5 μ g *Salmonella typhosa* lipopolysaccharide, or no mitogen or antigen. Three days after infection, cells were injected into BALB/c or nude mice; resultant tumors were classified, and cells were karyotyped. Lymphoma developed in 100% of the mice receiving cells treated *in vitro* with Abelson virus plus antigen or mitogen. The tumors, appearing a minimum of 29 days after inoculation, involved the lymph nodes, occasionally the spleen, and were all readily transplantable. The predominant cell type had deeply indented nuclei and no cytoplasmic granules. The results indicate that stimulation of DNA synthesis with mitogen or appropriate antigen was necessary for tumorigenesis by spleen cells undergoing *in vitro* infection with Abelson virus. There were no significant variations in the latent period correlated with species or sex. That some of the tumors were of donor origin as shown by female donor karyotypes among tumor cells developing in male hosts, indicates that cells infected by virus *in vitro* were transformed. It was thus shown that it is possible to infect spleen cultures with Abelson leukemia virus, to obtain lymphomas upon subsequent transfer of the cells to mice, and to employ such experiments as a tool for the *in vitro* study of transformation of lymphocytes by leukemia viruses.

- 6830 ADENOVIRUS TYPE 2 DNA REPLICATION: II. TERMINI OF DNA REPLICATION. (Eng.) Schilling, R. (Inst. Genetics, Univ. Cologne, Cologne, Germany); Weingartner, B.; Winnacker, E.-L. *J. Virol.* 16(4):767-774; 1975.

The temporal order of synthesis of different regions of the adenovirus type 2 (Ad2) viral chromosome was studied by an analysis of the distribution of radioactivity in restriction enzyme fragments from mature viral DNA synthesized during [3 H]thymidine pulses of varying length in infected HeLa cells. After pulse-labeling, the viral DNA was isolated from the infected cells and analyzed by restriction endonuclease digestion, gel electrophoresis, and chromatography on benzoylated-naphthoylated DEAE-cellulose. Complete, mature Ad2 DNA molecules were isolated from infected HeLa cells which had been pulse-labeled at 20 hr postinfection in pulse periods shorter than the time necessary for the completion of one round of viral DNA replication. That the mature viral DNA had been cleanly separated from the replicating forms was confirmed by gel electrophoresis and elution on 1 M NaCl and 1 M NaCl-2%

caffeine. After digestion with the restriction endonucleases Eco RI, Hpa I, and Hind III, a temporal order of synthesis of different regions of the viral genome was established from the relative specific radioactivities in the restriction enzyme fragments. A comparison with the physical order of these fragments revealed the existence of two termini of DNA replication towards both the molecular right and left ends, respectively, of the viral chromosome. Ad2 DNA replication thus occurs bidirectionally. Because the increase in relative specific activity per unit length of viral DNA was similar in both the left and the right gradient, the rates of replication in both directions must be very similar. The data are consistent with bidirectional replication starting either internally or at both ends of the Ad2 DNA molecule.

- 6831 LYMPHOID LEUKOSIS IN CHICKENS CHEMICALLY BURSECTOMIZED AND SUBSEQUENTLY INOCULATED WITH BURSA CELLS. (Eng.) Purchase, H. G. (U. S. Dept. Agriculture, ARS, Natl. Program Staff, Livestock and Veterinary Sciences, Beltsville, Md. 20705); Gilmour, D. G. *J. Natl. Cancer Inst.* 55(4): 851-855; 1975.

A study was undertaken to determine whether cyclophosphamide (CY) would eliminate lymphoid leukosis (LL), a neoplasm of the bursa-dependent lymphoid cells of the chicken, and whether syngeneic transfer of bursa lymphoid cells to CY-treated chickens would replace the target cells and thus restore susceptibility to LL. LL was induced by Rous-associated virus-1 in susceptible chickens. CY (2.5 or 4 mg, intraabdominally, on days 1-4 of hatching), which destroyed the lymphoid elements of the bursa of Fabricius and abrogated humoral immunity, prevented LL. Concomitantly, osteopetrosis and other neoplasms increased. Transfer of bursa cells from chickens into CY-treated hatchmates restored immune competence. Birds whose B-cell functions were reconstituted died of LL and were less likely to die of osteopetrosis and other neoplasms than were CY-treated chicks. These results suggest that the bursa cell transferred into the CY-treated chicks were the target cells for lymphoid leukosis transformation.

- 6832 TEMPERATURE-SENSITIVE MUTANTS OF SOMATIC MAMMALIAN CELLS. (Eng.) Basilico, C. (New York Univ. Sch. Medicine, New York, N.Y. 10016). *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 41-45.

Temperature sensitive (ts) mutants of somatic mammalian cells have been studied to elucidate the basic changes characterizing the neoplastic cell. The isolation and characterization of ts mutants of the BHK21 hamster fibroblast line is reviewed. The first mutant characterized was designated ts422E; it appears to have a specific defect in the production of the 32S RNA precursor, probably due to the formation of an aberrant 32S RNA con-

taining preribosomal particle. This mutant should be useful for studies on the relation between cell proliferation and ribosomal RNA synthesis and protein synthesis in that the cessation of growth of this mutant at the nonpermissive temperature does not result from an overall arrest of protein synthesis. It appears that the concentration of some critical protein is too low in these cells and does not allow the formation of a proper mitotic spindle. As a consequence, kariokinesis is grossly affected. The result of a specific *ts* defect on the progress of the cell through the mitotic cycle was also studied in the AF8 mutant. At the nonpermissive temperature, *ts*AF8 cells become arrested in the G1 phase of the mitotic cycle, the cycle arrest point being located in G1 somewhere between the blocks induced by serum starvation and that induced by isoleucine deprivation. The synthesis of mitochondrial DNA is not affected. The multiplication of Adenovirus 2 in the *ts* BHK mutants was studied. In *ts*422E and another mutant virus, multiplication was not affected by temperature, whereas two other mutants showed a reduction in yield at the nonpermissive temperature. In the *ts*AF8 mutant, the virus did not multiply at the nonpermissive temperature but grew normally at the permissive temperature. The block to adenovirus multiplication seemed to be at the level of viral DNA synthesis and to be expressed even earlier and more stringently than the block to cell DNA synthesis. Thus, the gene product affected by the *ts*AF8 mutation appears to be necessary for cell DNA synthesis only once and it seems to be necessary to allow entering into the S phase of the cycle. The use of genetic tools such as the *ts* mutants should contribute valid knowledge to the study of growth regulation and cancer.

- 6833 VIRUS SPECIFIC RNA IN HAMSTER CELLS ABORTIVELY INFECTED WITH HUMAN ADENOVIRUS TYPE 12. (Eng.) Mak, S. (Biology Dept., McMaster Univ., Hamilton, Ontario, Canada). *Virology* 66(2):474-480; 1975.

Viral RNA synthesis in hamster embryo cells abortively infected with human adenovirus type 12 (Ad 12) was compared with that of "early" viral RNA synthesized in lytically infected KB cells. Hamster embryo cells in Alpha-minimal essential medium (1.5×10^7 cells/8 ml) were infected with 2,500 virions/cell corresponding to about 1 plaque-forming U/cell. KB cells were infected in suspension (10^7 cells/ml) with 1,000 virions/cell and diluted to 3×10^5 cells/ml for further incubation. Hamster embryo cells abortively infected with Ad 12 synthesized only a small amount of virus-specific RNA up to 30 hr after infection, whereas the lytically infected KB cells synthesized a high proportion of virus-specific RNA by 30 hr postinfection. Some of the characteristics of the viral RNA were compared with those of "early" viral RNA from infected KB cells. It was found that (i) they had the same average guanine plus cytosine content as estimated by melting profiles of DNA-RNA hybrids; (ii) they had similar size distribution; and (iii) they contained very similar nucleotide sequences as determined by competition-hybridization experiments. The size distribution of virus-specific RNA in the infected hamster cells was almost identical

to that of "early" AD 12 virus-specific RNA in productively infected KB cells. The pattern of viral RNA synthesis changed little between 16-30 hr post-infection in hamster cells.

- 6834 RNA-DIRECTED DNA POLYMERASE ACTIVITY OF RETICULOENDOTHELIOSIS VIRUS: CHARACTERIZATION OF THE ENDOGENOUS AND EXOGENOUS REACTIONS. (Eng.) Waite, M. R. F. (Dept. Microbiology, Univ. Texas, Austin, Tex. 78712); Allen, P. T. *J. Virol.* 16(4):872-879; 1975.

The RNA-directed DNA polymerase activity of reticuloendotheliosis virus (REV) was characterized. REV and Rous-associated virus-1 [RSV(RAV-1)] were grown in subconfluent chicken embryo cells and purified by sedimentation through a glycerol cushion. Standard exogenous and endogenous DNA polymerase assays were performed as were a simultaneous detection assay and hybridization experiments using an ^3H -DNA probe and purified REV and RSV(RAV-1) RNA. Serologic studies were also performed to determine whether the endogenous DNA polymerase activity of the REV preparations was due to contamination by avian leukosis viruses. Both the endogenous and exogenous DNA polymerase activities exhibited up to 10-fold greater activity at the optimum concentration of Mn^{2+} (0.025 mM for exogenous; 0.25 mM for endogenous) than at any concentration of Mg^{2+} . Antiserum to the DNA polymerase of an REV group virus (spleen necrosis virus) inhibited both the endogenous and exogenous enzyme activity of REV, whereas antiserum to RSV(RAV-1) DNA polymerase did not. The DNA product of the endogenous reaction was associated with the high-molecular weight of REV and annealed with REV RNA but not with RSV(RAV-1) RNA. These data combined with previous observations suggest that the REV group may not be avian viruses that coevolved with their hosts; REV could be a mammalian virus which has only relatively recently begun to infect birds.

- 6835 PLAQUE ASSAY OF AVIAN SARCOMA VIRUSES USING CASEIN. (Eng.) Balduzzi, P. C. (Univ. Rochester Sch. Medicine and Dentistry, Rochester, N.Y. 14642); Murphy, H. *J. Virol.* 16(3):707-711; 1975.

There is a relationship between the transformation of secondary cultures of chick embryo fibroblasts by Rous sarcoma virus (RSV) and the induction by the virus of the ability of the cells to cause the lysis of casein added to the nutrient agar medium. Caseinolytic activity is not induced by viruses which do not transform the cells *in vitro*, i.e. avian leukosis virus. The induction of caseinolytic activity in cells infected with RSV mutants temperature-sensitive for transformation is not affected by temperature to as great an extent as are the transformation-related morphological changes. However, the transformation and induction characteristics are always found to be associated, and it is suggested that both are functions of a single viral gene. The induction of caseinolytic ability is easily monitored; lysis produces distinct clear areas in the turbid casein-agar gel. This assay could be useful for the

quantitation of those viral transforming agents that do not produce easily-detectable foci of transformed cells during *in vitro* studies.

- 6836 ALTERATIONS IN THE RELATIVE AMOUNT OF SEPARATE FRACTIONS OF LOW MOLECULAR WEIGHT NUCLEAR RNAs IN TUMOR TISSUES. (Rus.) Kozlov, A. P. (The N. N. Petrov Res. Inst. of Oncology of the U.S.S.R. Ministry of Health, Leningrad, U.S.S.R.); Pljusnin, A. Z.; Knjazev, P. G.; Kuznetsov, O. K.; Seits, I. F. *Vopr. Onkol.* 21(6):96-101; 1975.

Qualitative and quantitative differences were studied in low molecular weight nuclear RNA fractions in normal rat liver cells and in Zajdela hepatoma, and in the total cellular RNAs in normal mouse spleen, NK/Ly ascites tumor, as well as in normal and Rous sarcoma virus-transformed chicken fibroblasts by electrophoretic method in 8% and 15% polyacrylamide gels. No qualitative differences in terms of electrophoretic mobility and the number of low molecular weight RNA fractions were observed. Significant increase in the quantity of the RNA fraction separated by electrophoresis (U3) was observed in Zajdela hepatoma and NK/Ly ascites tumor cell nuclei as compared with the corresponding normal cell nuclei. The increase in the U3 RNA fraction can be related to an enhancement of ribosomal RNA synthesis. The findings obtained concerning virus-transformed chicken fibroblasts may indicate an excessive synthesis of low molecular weight viral RNAs during the process of virus replication. The quantitative changes observed appear to be of particular interest since low molecular weight nuclear RNAs are likely to perform regulatory functions.

- 6837 TRANSLATION OF ROUS SARCOMA VIRUS RNA IN A CELL-FREE SYSTEM FROM ASCITES KREBS II CELLS. (Eng.) Von Der Helm, K. (Institut Suisse des Recherches Experimentales sur le Cancer, Lausanne, Switzerland); Duesberg, P. H. *Proc. Natl. Acad. Sci. USA* 72(2):614-618; 1975.

The template activities of the 60-70S RNA complex and of the 30-40S subunit RNA species of Rous sarcoma virus were tested in a cell-free protein-synthesizing system from mouse ascites Krebs II cells. Stimulation of protein synthesis over the endogenous background was about 2-fold with 30-40S viral RNA and about 1.3-fold with 60-70S viral RNA as template. Analysis by sodium dodecyl sulfate-gel electrophoresis showed that the predominant polypeptide synthesized *in vitro* in response to 30-40S RNA of Rous sarcoma virus had a molecular weight of 75,000-80,000. This polypeptide could be precipitated by antiserum against the group-specific antigens of the virus, although its molecular weight was higher than that of virion group-specific antigen proteins. Analysis of tryptic digests of the protein made *in vitro* indicated similarity to tryptic digests from authentic virion group-specific proteins. It is concluded that part of the RNA from Rous sarcoma virus is translated *in vitro* into a high-molecular-weight protein, perhaps a precursor of the virion group-specific proteins.

- 6838 SURFACE RUFFLES AS MARKERS FOR STUDIES OF CELL TRANSFORMATION BY ROUS SARCOMA VIRUS. (Eng.) Ambros, V. R. (Dept. of Biology, Massachusetts Inst. of Technology, Cambridge, Mass. 02139); Bo Chen, L.; Buchanan, J. M. *Proc. Natl. Acad. Sci. USA* 72(8):3144-3148; 1975.

Confluent chick embryo fibroblasts infected with the Ts68 mutant of Rous sarcoma virus were examined by scanning electron microscopy at the permissive (36 C) and nonpermissive (41 C) temperatures for transformation. Infected cells but not mock-infected cells, shifted from 41 to 36 C changed from elongated to rounded. This was preceded by the appearance of surface ruffles on the cell. These surface ruffles were not observed on cells maintained at 41 C, and appeared as early as 0.5 hr after a shift to 36 C. After two hr, more than 70% of the cells had ruffles. By 3.5 hr after the shift from 41 to 36 C, cultures were fully transformed by the criteria of cell roundness and the presence of surface ruffles. This surface ruffling of cells is the earliest event so far reported during the transformation process and is not dependent upon protein synthesis as indicated by the lack of effect of cycloheximide on rounding or ruffling of the cells. It appears that a temperature-sensitive initiator of surface changes exists in the infected cells held at 41 C.

- 6839 A STRUCTURAL CHANGE OF THE PLASMA MEMBRANE INDUCED BY ONCOGENIC VIRUSES: QUANTITATIVE STUDIES WITH THE FREEZE-FRACTURE TECHNIQUE. (Eng.) Torpier, G. (Département de Virologie, Institut Pasteur 25, rue du Dr Roux, 75015 Paris, France); Montagnier, L.; Biquard, J. M.; Vigier, P. *Proc. Natl. Acad. Sci. USA* 72(5):1695-1698; 1975.

The density of intramembranous particles (IM particles) were studied quantitatively by a freeze-etching technique in mammalian and avian cell systems. Two clones were derived from the asparagine-dependent subclone C13/8 from BHK21/13 line hamster fibroblasts: (1) C13/8/HS5, transformed by hamster sarcoma virus, and (2) C13/8/SPy2, transformed by polyoma virus. A mutant of Schmidt-Ruppin strain of Rous sarcoma virus (RAV 1) was used for infecting and transforming secondary cultures of chick embryo fibroblasts (CEF). Hamster cells and CEF cells were harvested for freeze-fracturing. Thirty micrographs of each cell preparation were selected at random, and counts of $1 \mu m^2$ of each picture were statistically analyzed. No deviation from random distribution of IM particles was observed in the membrane fractures of normal or virus-transformed BHK21 cells. However, three times more particles were observed in the clone transformed by hamster sarcoma virus than in control cells. CEF infected with RAV 1 also demonstrated a significant increase in particle density. The increase in particles is either related to virus-induced transformation, or to virus production only. The authors suggest that the primary change induced by the virus may be due to the insertion of new proteins in the hydrophobic portion of the plasma membrane.

- 6840 ACTIVE INTERVENTION TO PREVENT CANCER *IN VIVO* WITH PROPHYLACTIC DRUGS. (Eng.) Apple, M. A. (Univ. California Medical Sch., San

Francisco, Calif. 94143). *J. Clin. Pharmacol.* 15(1): 29-35; 1975.

A variety of natural products, including Actinomycin-S2, Cinerubin, Axenomyacin, Rifamycin-dinitrophenylhydrazone, Streptovaricin-D, and Rifamycin-SV, were compared for their activity as inhibitors of Rous sarcoma virus reverse transcription *in vitro*. The 50% inhibitory concentration of Rous sarcoma virus reverse transcriptase ranged from 0.5-1.0 µg/ml for Actinomycin-S2 and Cinerubin to 500-1,000 µg/ml for Streptovaricin-D and Rifamycin-SV. The possibility of intervening and preventing virus-infected cells from transforming into cancer cells by using prophylactic drugs was studied by inoculating Rous sarcoma virus into 3- to 5-day-old specific pathogen-free Kimber white Leghorn chickens. Approximately 24 hr after virus inoculation, the chickens received either saline or drug ip. Animals were necropsied at four weeks, and the number of sarcomas was counted. The development of sarcomas in the drug-treated chickens appeared to correlate with the potency of the drug as a reverse transcription inhibitor. Streptovaricin-D and Rifamycin-SV were not significantly active against the virus *in vivo*, while Cinerubin and Actinomycin-S2 protected over 75% of the animals against sarcomas. It is suggested that drugs able to prevent cancer now exist, and that a molecular basis for their activity may be at the level of genetic transcription.

6841 TRANSPLANTATION OF HEPATOMAS INDUCED IN THE AVIAN LIVER BY MC29 LEUKOSIS VIRUS. (Eng.) Lapis, K. (Sennelweis Med. Univ., Budapest, Hungary); Beard D.; Beard, J. W. *Cancer Res.* 35(1): 132-138; 1975.

The establishment and characteristics of a transplantable hepatoma derived from virus-induced primary hepatic tumors are described. Tumor material was obtained from two chickens and was harvested 31 days after iv inoculation of 9×10^8 avian leukosis strain MC29 virus particles in chick embryo cells. Pieces of excised tumor were introduced into the abdominal cavity of Line 15 White Leghorn chicks. After the seventh passage, the tumor was inoculated im into one thigh, and in some cases was inadvertently lodged sc, where it grew rapidly. During the first three passages, chicks received cortisone (2.5 mg/kg/day ip) for three days after transplantation. Only half of each group received cortisone in subsequent transfers. The primary tumors were numerous, circumscribed grayish-white nodules (2-8 mm in diameter). In 35 experiments on 278 chicks receiving ip transplantation, 222 animals (80%) developed tumors in the presence or absence of cortisone. Tumors were palpable in most birds within 15-18 days. Animals developed either a single large, grayish-white nodule or hemorrhagic, bluish-red nodule (0.53 mm in diameter). The im transplants took regularly (67 positive of 69 implants) and grew with increasing rapidity with each passage. Tumors were highly vascularized and scattered, and yellowish, necrotic foci were numerous. Narrow fascicles of tumors invaded the muscle fibers which were frequently atrophic and disintegrating. The sc nodules were encapsulated. About 25% of animals in the im group had nodules metastatic to the

liver. Tumors of the first passage were hepatocellular carcinoma with well-differentiated structure. Transplant cells were cytologically identical to those of the primary tumor, and in further passages became more uniform, consisting of trabeculae that were two or more cells across. The microscopic appearance of the muscle tumors showed the same trabecular pattern and cytologic features. This is the first transplantable tumor of viral origin and has the advantage of marked transplantability and high incidence of growth in all sites of implantation.

6842 SPECIFIC BINDING OF TRYPTOPHAN TRANSFER RNA TO AVIAN MYELOBLASTOSIS VIRUS RNA-DEPENDENT DNA POLYMERASE (REVERSE TRANSCRIPTASE). (Eng.) Panet, A. (Center for Cancer Res., Massachusetts Ave., Cambridge, Mass. 02139); Haseltine, W. A.; Baltimore, D.; Peters, G.; Harado, F.; Dahlberg, J. E. *Proc. Natl. Acad. Sci. USA* 72(7):2535-2539; 1975.

An assay for high-affinity binding sites was used to determine whether the reverse transcriptase of avian myeloblastosis virus (AMV) has a specific binding site for tryptophan transfer RNA (tRNA^{Trp}). Purified AMV reverse transcriptase was incubated with ³²P-labeled RNA obtained from cultures of chicken embryo fibroblasts infected with the Schmidt-Ruppin D Rous sarcoma virus or Carr-Zilber-associated virus. After ten minutes incubation at 2 C, the reaction mixtures were chromatographed on columns of Sephadex G-100. The results indicated that of all the chicken tRNAs tested, only tRNA^{Trp} and a tRNA^{Met} bound to the AMV enzyme with high enough affinity to be selected from a mixture of chicken cell tRNAs. The ability of the tRNA^{Trp} to change the sedimentation rate of the reverse transcriptase indicated that tRNA^{Trp} was not binding to a contaminant in the enzyme preparation. Treatment of the enzyme with monospecific antibody to reverse transcriptase prevented the binding of tRNA and inhibited the DNA polymerase activity of the enzyme. The ability of reverse transcriptase to utilize tRNA^{Trp} as a primer for DNA synthesis therefore appears to involve a highly specific site on the enzyme.

6843 STUDY ON ANTIGEN APPEARANCE WITHIN THE MAREK HERPES VIRUS INFECTED CELL UNDER ARGININE DEFICIENCY. (Jpn.) Migai, H. (Sapporo Medical Univ., Sapporo, Japan). *Virus (Tokyo)* 24(1):96-99; 1974.

The influence of arginine (Arg) deficiency on the synthesis of the membrane antigen that appears in Marek disease herpes virus (MDHV)-infected cells was investigated. In addition, the relation between the time of appearance of the membrane antigen and viral antigen and the time of virus DNA synthesis and multinuclear cell formation was studied. Arg-deficient quail fibroblasts were injected with MDHV and cultured in Arg-deficient, normal, 5-iododeoxyuridine-containing, or puromycin-containing medium. The emergence of membrane antigens synthesized in Arg-deficient medium peaked at two intervals, 8 hr and 20 hr, after inoculation. However, in the continuous presence of

5-iododeoxyuridine the second period peak disappeared. In the presence of puromycin, the synthesis of this antigen was also remarkably suppressed. The fluorescent antibody method demonstrated that virus antigens were not synthesized in infected cells in Arg-deficient medium. Acridine orange staining showed that viral DNA synthesis did take place in this medium, reaching a plateau 36 hr after infection and continuing until 60 hr. Multinuclear cells formed even among infected cells in Arg-normal and -deficient media. In Arg-deficient medium, formation reached a peak after 24 hr. In the presence of LUDR or puromycin, few multinuclear cells were formed. The results suggest that the membrane antigens are formed before and after DNA synthesis and that there is a relation between antigens formed after DNA synthesis and the formation of multinuclear cells.

- 6844 HUMAN CYTOMEGALOVIRUS. III. VIRUS-INDUCED DNA POLYMERASE. (Eng.) Huang, E.-S. (Sch. Medicine, Univ. North Carolina, Chapel Hill, N.C. 27514). *J. Virol.* 16(2):298-310; 1975.

Human cytomegalovirus (CMV)-induced DNA polymerase and some host cell DNA polymerases were purified and characterized. Infection of WI-38 human fibroblasts with human cytomegalovirus (CMV) led to the stimulation of host cell DNA polymerase synthesis and induction of a novel virus-specific DNA polymerase. This cytomegalovirus-induced DNA polymerase was purified and separated from host cell enzymes by chromatography on DEAE-cellulose and phosphocellulose columns. It could be distinguished from host cell enzymes by chromatographic behavior, template primer specificity, sedimentation property, and the requirement of salt for maximal activity. This virus-induced enzyme had a sedimentation coefficient of 9.2S and was found in both the nuclei and cytoplasm of virus-infected cells, but not in uninfected cells. This enzyme could efficiently use activated calf-thymus DNA, poly(dA) x oligo(dT)₁₂₋₁₈, and poly(dC) x oligo(dG)₁₂₋₁₈ as template primers, especially poly(dA) x oligo(dT)₁₂₋₁₈, but it could not use poly(rA) x oligo(dT)₁₂₋₁₈, poly(rC) x oligo(dG)₁₂₋₁₈, or oligo(dT)₁₂₋₁₈. The enzyme required Mg²⁺ for maximal activity. It was sensitive to *p*-hydroxymercuribenzoate (0.25 mM), and was not a zinc metalloenzyme. In addition, the cytomegalovirus-induced DNA polymerase activity (0.25 mM) was enhanced by adding 0.06-0.12 M NaCl or 0.03-0.06 M (NH₄)₂SO₄ to the reaction mixture. The results (i.e., different chromatographic behavior, efficiency of poly(dA) x oligo(dT)₁₂₋₁₈ as template primers, and the nondetectability in uninfected cells) are all consistent with the hypothesis that this virus-induced DNA polymerase is coded by the virus genome. These observations do not, however, rule out the possibility that the appearance of this new DNA polymerase is due to the derepression of a host cell enzyme that is not detectable in normal cells or to a modification of a preexisting host enzyme as a result of virus infection.

- 6845 COMPARISON BETWEEN GROWTH CHARACTERISTICS OF AN EPSTEIN-BARR VIRUS (EBV)-GENOME-NEGATIVE LYMPHOMA LINE AND ITS EBV-CONVERTED SUB-

LINE *IN VITRO*. Steinitz, M. (Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden); Klein, G. *Proc. Natl. Acad. Sci. USA* 72(9): 3518-3520; 1975.

In vitro Epstein-Barr virus (EBV) infection of an EBV genome-negative lymphoma line (BJAB), derived from an African Burkitt lymphoma, yielded a subline (GC-BJAB) that contains one to two EBV genome copies/cell. The growth characteristics of the two lines were compared to determine the nature of the selective advantage conferred on lymphoid cells under *in vitro* conditions by the presence of the viral genome. BJAB cells grew well at 34 C, 37 C, and 39 C; GC-BJAB cells grew at 37 C and 39 C but did not grow or grew poorly at 34 C. At 37 C, GC-BJAB cells remained viable for a long time after reaching saturation density (approximately 10⁶ cells/ml). In contrast, BJAB cultures died rapidly after reaching similar maximum density. Since the presence of the EBV genome in the GC-BJAB line is the only known difference between the two lines, it is likely that the viral genome or its products brought about two changes: dependence on some limiting factor or condition that cannot be made at 34 C and increased resistance to saturation conditions. It is possible that cultivation at 34 C may favor the establishment of genome-negative lymphoma lines, in competition with contaminating genome-positive cells. Conversely, cultivation under saturation conditions may facilitate the emergence of EBV-converted cell lines from *in vitro* EBV-infected lymphoma lines and perhaps also the outgrowth of a permanent EBV-carrying lymphoblastoid line from normal lymphocytes.

- 6846 ULTRAVIOLET INACTIVATION OF EPSTEIN-BARR VIRUS: EFFECT ON SYNTHESIS OF VIRUS-ASSOCIATED ANTIGENS. (Eng.) Sairenji, T. (Kumamoto Univ. Medical Sch., Kumamoto, 860, Japan); Hinuma, Y. *Int. J. Cancer* 16(1):1-6; 1975.

The relative sensitivity to UV light of genome functions of the P3HR-1 strain of Epstein-Barr virus (EBV) was studied. One-milliliter samples of EBV were exposed to UV light for 1-10 min in an ice bath. Virus samples were mixed with C-6 cell suspensions and incubated at 37 C for two hours before antigen assays. The formation of viral capsid antigen (VCA) appeared to be more sensitive than that of early antigen (EA), while the synthesis of membrane antigen was most resistant, as seen on examination in the presence of cytosine arabinoside (Ara-C, 20 µg/ml). However, the appearance of both VCA and EA, but not that of membrane antigen, was delayed with UV-irradiated virus, in either the presence or absence of Ara-C. The synthesis of EA and VCA induced by UV-irradiated virus was thus suppressed in the presence of Ara-C, while that of membrane antigen was not. The Ara-C sensitive and delayed appearance of EA or VCA after infection with UV-damaged EBV may be explained by repair of the virus DNA mediated by the host cell, or complementation with the resident EBV genome of the C-6 cells.

- 6847 EPSTEIN-BARR VIRUS-INDUCED CAP FORMATION IN HUMAN LYMPHOBLASTOID CELLS. (Eng.) Hinuma, Y. (Kumamoto Univ. Med. Sch., Japan); Suzuki, M.; Sairenji, T. *Int. J. Cancer* 15(5):799-805; 1975.

Cap formation of Epstein-Barr virus (EBV) adsorbed to human lymphoblastoid cells was studied by indirect membrane immunofluorescence. EBV produced from the B95-8 marmoset cell line, and the human C-6 line derived from the NC-37 human lymphoblastoid cell line were used. The indirect membrane immunofluorescence procedure involved the adsorption of EBV on the cells incubated at 0 C and the reaction with anti-virus serum and anti-human immunoglobulin G. Cells were then outlined by "ring" fluorescence at 0 C. When the ring cells were warmed at 37 C, a "cap" fluorescence appeared. This cap formation was induced by EBV alone without the participation of antibodies involved in the immunofluorescence procedure. The cap cells decreased when the virus preparation was diluted. Qualitative changes appeared at 15 C, and maximal cap formation occurred at pH 7 and 8. The cap formation was reversibly inhibited by NaN_3 , NaCN , 2,4-dinitrophenol, D-glucose, D-mannose, and D-mannitol. The mechanism of EBV-induced cap formation is similar to that induced by other antibodies and ligands; therefore, certain viruses can induce redistribution and cap formation of receptors in certain cells.

- 6848 SENSITIVITY OF THE EPSTEIN-BARR VIRUS TRANSFORMED HUMAN LYMPHOID CELL LINES TO INTERFERON. (Eng.) Adams, A. (Dept. of Tumor Biology, Karolinska Inst. Stockholm 60, Sweden); Strander, H.; Cantell, K. *J. Gen. Virol.* 28(2):207-217; 1975.

The effect of interferon on the expression of Epstein-Barr virus (EBV) early gene functions was studied in various producer and nonproducer human lymphoid cell lines. All lines were positive for the EBV-determined nuclear antigen (EBNA), and were assumed to be transformed by EBV. Six superinfectable lymphoid cell lines (Raji, Daudi, NC-37, Maku, RPMI 6410, and Odour) were treated with human WBC interferon, human fibroblast interferon, or mock interferon preparations; they were then infected with EBV. The effects on early antigen (EA) synthesis, the expression of intrinsic EBV genomes, and cell growth were determined. The effect of interferon pretreatment on the growth of vesicular stomatitis virus (VSV) was studied in Raji and Daudi cells. In all six cell lines tested, interferon suppressed EA synthesis, but the different cell lines showed a wide variation in sensitivity to interferon. The lines also differed greatly with respect to the inhibitory influence of interferon on VSV expression, VSV being more sensitive to the antiviral action of interferon than EBV. EA synthesis following 5-iododeoxyuridine (25 $\mu\text{g}/\text{ml}$) induction was as sensitive to interferon inhibition as was the EA synthesis observed after EBV superinfection. The spontaneous EA expression which occurs in a small percentage of the cells in the producer cell lines (e.g., Maku) was not blocked by interferon pretreatment. Six cell lines originally established from Burkitt lymphoma biopsies were growth inhibited by low concentrations of interferon,

the inhibitory effect being seen only after at least 3-4 days of incubation. The block in cell multiplication could be reversed by washing the cells. Eight other cell lines grew normally in the presence of interferon. A good correlation existed between the antiviral and growth responses of the various lines tested. The antiviral and growth inhibitory activities of different interferon preparations could not be separated. Final proof that the anti-growth substance is interferon itself will require access to interferon purified to homogeneity.

- 6849 SPONTANEOUS AND INDUCED MUTAGENESIS IN WESTERN EQUINE ENCEPHALOMYELITIS VIRUS IN CHICK EMBRYO CELLS WITH DIFFERENT REPAIR ACTIVITY. (Eng.) Dubinin, N. P. (Inst. General Genetics, U.S.S.R. Acad. Sciences); Zasukhina, G. D.; Nesmashnova, V. A.; Lvova, G. N. *Proc. Natl. Acad. Sci. USA* 72(1):386-388; 1975.

The survival rate of Western equine encephalomyelitis virus was studied in commercial and leukosis-free chick embryo cells after UV irradiation (4.6 erg/mm^2) and methyl methanesulfonate (MMS, 2×10^{-3} M) treatment. The virus dose was 1-5 plaque-forming U/cell. In both the MMS and UV irradiation experiments, the virus survival rate was higher in the leukosis-free embryo cells. This is attributed to the fact that these cells possess active DNA and RNA repair systems. In commercial chick embryos, the RNA repair system is inactive. The levels of spontaneous mutagenesis (on the basis of the yield of small plaque variants of the encephalomyelitis virus) did not essentially change when the virus was passaged in leukosis-free chick embryo cells, whereas an increase in the number of small plaque variants was observed in the cells of commercial chick embryos. A ten-fold increase in the number of induced virus variants was observed in commercial chick embryo cells in experiments with MMS, as compared with the control, whereas the induction of virus variants was not noted in leukosis-free cells. The data suggest that differences in RNA repair activity can influence the survival of and levels of spontaneous and induced mutability in an RNA virus.

- 6850 ANTIBODIES TO HERPES SIMPLEX VIRUS IN JEWISH WOMEN WITH CERVICAL CANCER AND IN HEALTHY JEWISH WOMEN OF ISRAEL. (Eng.) Menczer, J. (Chaim Sheba Med. Cent., Tel Hashomer, Israel); Leventon-Kriss, S.; Modan, M.; Oelsner, G.; Richter, C. B. *J. Natl. Cancer Inst.* 55(1):3-6, 1975.

Herpes simplex virus (HSV) antibody titers were examined in sera from 39 Israeli Jewish women (all but one older than 40 yr) with squamous cell carcinoma of the uterine cervix (CaCx) and in sera from controls matched by age and country of origin. Highly significant differences were found between the cases and controls for both HSV type 1 (HSV-1) and HSV type 2 (HSV-2). The geometric-mean titer (GMT) among the CaCx patients was 1235 for HSV-1 and 86 for HSV-2. In the control group, the GMT for HSV-1 was 425 and for HSV-2, 22. Compared to findings in other demographic areas, the GMT of HSV-1 among the CaCx cases

was considerably higher, whereas the GMT for HSV-2 was in the same range. The percentage of HSV-2 positive patients, as defined by the HSV-2/HSV-1 antibody titer ratio, was low compared to that found in other demographic areas; this was presumably due to the high incidence of HSV-1 infection in the population. The HSV-1 and HSV-2 infection rate in the Israeli Jewish female population was estimated by antibody titers for 94 healthy subjects (aged 17-81 yr). The GMT of HSV-1 was considerably higher, whereas the GMT of HSV-2 was lower, than those reported elsewhere. The titers showed a gradual rise with age. Among 30 Jewish prostitutes aged 17-24 yr, the percentage of HSV-2 antibody titers of 640 or greater was significantly higher than in the healthy subjects. This finding indicates that Jewish women are not unusually resistant to HSV-2. The low incidence of CaCx among Jewish women might be explained by the low incidence of HSV-2 infection in the Jewish population.

6851 INHIBITION OF DNA POLYMERASE FROM HERPES SIMPLEX VIRUS-INFECTED WI-38 CELLS BY PHOSPHONOACETIC ACID. (Eng.) Mao, J. C. H. (Abbott Lab., North Chicago, Ill.); Robishaw, E. E.; Overby, L. R. *J. Virol.* 15(5):1281-1283; 1975.

The differential sensitivity of DNA polymerase of Herpes simplex virus (HSV)-infected Wi-38 cells and normal cells to phosphonoacetic acid was investigated. The cells were lysed and the polymerases from both cultures were purified using *O*-(diethylaminoethyl)cellulose, phosphocellulose and Sephadex G-200. The HSV-induced DNA polymerase differed from normal Wi-38 polymerase in the following ways: (1) HSV polymerase eluted at a lower salt concentration, (2) KCl stimulated HSV polymerase but inhibited host polymerase, (3) optimal Mg^{2+} concentrations were different, (4) 0.2 mM MnCl completely inhibited HSV polymerase, but only by 35% in host polymerase, (5) HSV polymerase was more insensitive to inactivation by *N*-ethylmaleimide, and (6) the saturation concentration of activated calf thymus DNA as primer was 3 μ g/ml for HSV polymerase but was 50 μ g/ml for Wi-38 polymerase. The HSV-induced enzyme was extremely sensitive to phosphonoacetic acid with a 50% inhibition at 0.2 μ g/ml, while Wi-38 enzyme remained insensitive. Phosphonoacetic acid, at 0.3 μ g/ml, inhibited the HSV-induced polymerase by about 70% at DNA levels from 0.6 to 300 μ g/ml. The greater sensitivity of HSV-infected cells to phosphonoacetic acid, compared to normal cells, is confirmed.

6852 TEMPERATURE-SENSITIVE MUTANTS OF HERPES SIMPLEX VIRUS TYPE 1 DEFECTIVE IN LYSIS BUT NOT IN TRANSFORMATION. (Eng.) Hughes, R. G., Jr. (Dept. Medical Viral Oncology, Roswell Park Memorial Inst., Buffalo, N.Y. 14263); Munyon, W. H. *J. Virol.* 16(2):275-283; 1975.

Twelve temperature sensitive (ts) mutants of herpes simplex virus type 1 (HSV-1) were studied to determine whether or not particular mutants of HSV alter the ability of the virus to transform thymidine kinaseless L (Ltk⁻) cells to a tk-positive (Ltk⁺) phenotype. The mutants represented seven comple-

mentation groups, and were isolated subsequent to 5-bromodeoxyuridine (5 μ g) mutagenesis. These mutants were identified by their inability to replicate in a line of monkey (CV-1) cells at 39 C. Seven of these mutants, representing six complementation groups, induced thymidine kinase (tk) and transformed Ltk⁻ cells to a tk⁺ phenotype at both the permissive (34C) and nonpermissive (39C) temperatures. Thus, the defective cistrons in these six complementation groups, although necessary for lysis, have no essential function in this transformation system. Transformation by the 12 mutants was dependent on prior UV irradiation. Infection of cells with unirradiated virus under conditions that did not permit virus replication was not sufficient to allow cell transformation. Five mutants, representing two complementation groups, were tk⁻ and were incapable of causing the tk⁻-to-tk⁺ transformation at either 34 C or 39 C. The tk defects in these mutants are probably unrelated to the ts defects, since one of these complementation groups contains a tk⁺ member. Therefore, transformation of Ltk⁻ cells to a tk⁺ phenotype HSV-1 requires an active viral tk gene. One complementation group was represented by a single tk⁻ member. The role of this cistron in transformation remains undetermined because the primary block to transformation is presumed to be the tk⁻ phenotype. Mutants representing the seven complementation groups were unable to replicate at 39 C in two lines of HSV-1-transformed cells, indicating that the activities of resident wild-type copies of the defective cistrons, if present, could not be detected by complementation.

6853 INDUCTION OF HUMAN CELL DNA SYNTHESIS BY HERPES SIMPLEX VIRUS TYPE 2. (Eng.) Melvin, P. (Bowman Gray Sch. Med., Wake Forest Univ., Winston-Salem, N.C.); Kucera, L. S. *J. Virol.* 15(3):534-539; 1975.

Experiments were designed to determine the effect of nonpermissive temperature (42 C) on DNA synthesis in herpes simplex virus type 2-infected human embryonic fibroblasts. The MS, ANG and HOF strains of virus were used. Human embryonic fibroblast cultures incubated at nonpermissive temperatures for 48 hr and then shifted down to permissive temperature (37 C) for 72 hr showed an approximate 2-fold stimulation of [methyl-³H]thymidine ([³H]TdR) incorporation into DNA of infected cells in comparison with mock-infected cells on isopycnic gradient centrifugation. Analysis of the DNA species indicated a single peak of labeled DNA (density 1.688 g/cm³) from mock-infected cells. The profile of labeled DNA from infected cells showed a single major peak with a density (1.688 g/cm³) corresponding to host cell DNA, indicating a 2- to 4-fold increase in the amount of [³H]TdR incorporated into DNA from infected cells, compared with mock-infected cells. Confluent monolayers of fibroblasts cells were infected or mock-infected and incubated with medium supplemented with 0.2% fetal calf serum. [³H]TdR incorporation into total DNA in mock-infected cells was inhibited, whereas significant incorporation of the labeled precursor into DNA with a density of 1.688 g/cm³ still occurred in virus-infected cells. After incubation of virus-infected and mock-infected

cultures at 42 C to block viral DNA synthesis, the cultures were shifted down to 37 C to measure [^3H]-TdR incorporation into DNA and to enumerate the viable cells per culture. Incorporation into DNA of mock-infected cells was negligible, compared to the marked stimulation of [^3H]TdR incorporation into DNA of infected cells. Virus inactivated by UV irradiation, heat (56 C for 30 min), or neutral red dye and light did not induce cellular DNA synthesis, suggesting that an active viral genome was necessary for induction. These data suggest that induction of host-cell DNA synthesis by the herpes simplex virus type 2 is a function that may be related to the oncogenic activity of herpesviruses.

- 6854 WARTS IN SHEEP: IDENTIFICATION OF A PAPILLOMA VIRUS AND TRANSMISSION OF INFECTION TO SHEEP. (Eng.) Gibbs, E. P. J. (Animal Virus Res. Inst., Pirbright, Woking, Surrey, England); Smale, C. J.; Lawman, M. J. P. *J. Comp. Pathol.* 85(2):327-334; 1975.

Warts taken from three sheep were examined for virus by negative-contrast electron microscopy. Particles similar in size and symmetry to papilloma viruses were seen in all three warts examined. The definition of the structure of the viruses was poor in all the specimens, although a substructure resembling virus capsomeres could be identified in some particles. Attempts were made to reproduce the disease in experimental animals by inoculating 10% suspensions of the wart tissues in phosphate-buffered isotonic saline. Sheep and goats were inoculated by swabbing the tissue suspensions on the axillary and inguinal skin; cattle were inoculated id on the neck with 0.1 ml at each of 12 sites. Litters of neonate hamsters were inoculated sc over the thorax with 0.05 ml of tissue suspension. The disease was reproduced in sheep. The cattle and goats were refractory to infection, but in the neonate hamsters the virus produced slowly growing fibromas. However, no virus could be detected by electron microscopy in the fibromas. The viral etiology of the warts was established by the successful transmission of the disease to sheep with cell- and bacteria-free inocula prepared from the warts of the original sheep, and by the identification of virus particles conforming to the morphology of the papilloma virus subgroup in the naturally occurring and experimentally produced warts.

- 6855 SURFACE CARBOHYDRATES OF HAMSTER FIBROBLASTS. II. INTERACTION OF HAMSTER NIL CELL SURFACES WITH *RICINUS COMMUNIS* LECTIN AND CONCAVALIN A AS REVEALED BY SURFACE GALACTOSYL LABEL. (Eng.) Gahmberg, C. G. (Sch. Public Health, Univ. Washington, Seattle); Hakomori, S. *J. Biol. Chem.* 250(7):2447-2451; 1975.

The interaction of hamster NIL cell surfaces with *Ricinus communis* lectin and concanavalin A as evidenced by altered surface galactosyl label is described. Cells were incubated in phosphate-buffered isotonic saline (PBS) and 10 U of galactose oxidase. Without addition of D-galactose, cells which were pretreated with *Ricinus communis* agglutinin I adhered strongly and were difficult to separate from the

plates. The cells were labeled with 0.5 mCi/50 μl tritiated sodium borohydride. Two major galactoprotein labels were detected on the cell surface: galactoprotein a (apparent molecular weight 200,000) and galactoprotein b (apparent molecular weight 130,000). The labeling ([^3H]-formaldehyde) in galactoprotein a of NIL cells was greatly suppressed by pretreating cells with a high concentration (100 $\mu\text{g}/\text{ml}$) of *Ricinus communis* lectin or concanavalin A, whereas the label in it was greatly enhanced with a low concentration (10 $\mu\text{g}/\text{ml}$) of the lectins. The label in galactoprotein b of NIL cells was less affected by pretreatment with lectins. In NILpy cells the label in galactoprotein a was absent and the label in galactoprotein b was enhanced by pretreating cells with lectins at low concentrations, but it was suppressed at high concentrations. After treatment with lectins, the glycolipids of normal NIL cells, but not NILpy cells, became exposed as evidenced by enhanced labeling, possibly because of glycoprotein clustering. The results indicate that NIL cells mainly interact with the lectins through galactoprotein a, whereas NILpy cells interact with the lectins through galactoprotein b. The results support the view that specific, well defined glycoproteins are the binding sites for lectins, and that these interacting glycoproteins are qualitatively different in normal and transformed cells.

- 6856 UPTAKE PATTERNS AND TRANSPORT ENHANCEMENTS IN CULTURES OF HAMSTER CELLS DEPRIVED OF CARBOHYDRATES. (Eng.) Ullrey, D. (Massachusetts Gen. Hosp., Boston); Gammon, M. T.; Kalckar, H. M. *Arch. Biochem. Biophys.* 167(2):410-416; 1975.

Carbohydrate uptake and the effect of carbohydrate deprivation on the active transport of an amino acid analogue on transformed and untransformed hamster NIL cell lines were studied. NIL and polyoma-transformed NIL (py-NIL) were incubated with 1 mg/ml galactose (Gal), glucose (Glc), fructose (Fru), D-xylose, glucosamine (Glcam), or without carbohydrate (CH_2O) for 24 hr, and D-[U- ^{14}C]Gal and [^{14}C]cycloleucine uptakes were studied. Gal-uptake tests were performed at 23 C for 20 min with 1.6×10^{-5} M D-[U- ^{14}C]Gal. Cycloleucine uptake tests were performed at 22 C for 10 min with 3×10^{-5} M [^{14}C]cycloleucine. CH_2O -NIL cultures exhibited a markedly higher rate of Gal uptake (0.692 nM/mg cell protein accumulated in 20 min) than Gal-fed cultures (0.233 nM/mg) and Glc-fed cultures (0.170 nM/mg). Although py-NIL cultures fed Gal and Glc had a high uptake (0.506 and 0.583 nM/mg, respectively), CH_2O -py-NIL uptake was further enhanced (0.806 nM/mg). If Glc was lowered to 0.1 mg/ml in culture, NIL cultures acted similar to those of CH_2O -cultures (0.5 nM/mg in 20 min). Gal in the medium had to be lowered to 10 $\mu\text{g}/\text{ml}$ for NIL to act similar to CH_2O -cultures (0.58 nM/mg). Gal and Glcam acted similarly to Glc in affecting uptake (Glc was 70% Gal-induced uptake; Glcam was 80% Gal-induced uptake) in NIL cells. Fru (250% Gal-induced uptake), D-xylose (240%) and pyruvate (320%) demonstrated the CH_2O pattern (350%). Active transport of cycloleucine was enhanced by CH_2O (5.60 nM/mg/10 min in NIL, and 6.181 in py-NIL). Carbohydrate deprivation in NIL and py-NIL resulted in enhancement of the active transport of cycloleucine suggesting that this is independent of carbohy-

drate metabolism and glycolysis. Deprivation also resulted in increased uptake of carbohydrate on reexposure.

- 6857 *IN VITRO* POLYOMA DNA SYNTHESIS: INHIBITION BY 1- β -D-ARABINOFURANOSYL CTP. (Eng.) Hunter, T. (Armand Hammer Cent. Cancer Biol., Salk Inst., San Diego, Calif.); Francke, B. *J. Virol.* 15(4):759-775; 1975.

The effects of 1- β -D-arabinofuranosyl CTP (ara-CTP) on DNA replication were studied in an *in vitro* system from polyoma-infected BALB/3T3 cells. *In vitro* DNA synthesis in concentrated lysates of polyoma ts1260-infected 3T3 cells was found to be completely and instantaneously inhibited at any time during the reaction by the addition of 150 μ M ara-CTP; 0.3 μ M had no inhibitory effect, while intermediate concentrations resulted in a concentration-dependent reduction. Concomitant incorporation of [3 H]TTP and α - 32 P ara-CTP was observed, with the α - 32 P label found in both viral and cellular DNA. Even under inhibiting conditions, the ara-CTP is not preferentially located at the 3' end of the product DNA. Despite the high inhibition of total virus DNA synthesized, some form I DNA was formed at 20 μ M ara-CTP; this indicates that form I DNA has a supercoiled tertiary structure that denatures to a rapidly-sedimenting form. Replicating viral DNA showed an increase in the percentage of label in short chains pulse labeled in the presence of 7.5 μ M ara-CTP, as compared to controls. Chase of pulse-labeled short chains in the presence of excess dCTP illustrated that the preferential labeling of short chains did not result in an accumulation of such chains in the final product. It was demonstrated that the short chains made in the presence of ara-CTP were of smaller size than in the control; gel electrophoresis and density gradients suggested that the shorter size is not a consequence of close spacing on the template strand. In addition, it was concluded that actinomycin D exerts a general inhibitory effect on polyoma DNA synthesis. The results indicate three DNA polymerizing processes: continuous elongation of one strand; synthesis of the first two-thirds of the short chains; and completion of the short chains. The first and third steps are more sensitive to ara-CTP than the second step.

- 6858 THE SYNTHESIS AND TURNOVER OF VIRUS-SPECIFIC POLYADENYLATED RNA IN POLYOMA-INFECTED CELLS. (Eng.) Rutherford, R. B. (Univ. Rochester Sch. Med. Dent., N.Y.); Hare, J. D. *Biochem. Biophys. Res. Commun.* 62(4):789-797; 1975.

The synthesis and turnover of virus-specific polyadenylated RNA was investigated in mouse embryo cells infected with the 3049 strain of polyoma virus. Cultures were infected with virus and treated with fluorodeoxyuridine (FdU) (15 μ g/ml) for 24 hr. The FdU block was reversed at 24 hr after infection by treating with 20 μ g/ml thymidine, and the cells were subsequently harvested at 4-hr intervals. The cells contained several-fold more virus-specific polyadenylated RNA beginning between 4 and 8 hr after the

onset of viral DNA synthesis than did cells infected with wild type virus (1pS). Following infection with either virus strain, there was an identical small but significant enhancement of the level of total polyadenylated RNA measured by binding of 125 I-labeled RNA to poly(dT)cellulose. The polyadenylation of early virus-specific RNA was inhibited 85-90% by treatment with 50 μ g/ml cordycepin for 24 hr. This resulted in an early RNA preparation which competed fully with polyadenylated early virus-specific RNA in a ternary complex assay. Utilizing the nonpolyadenylated early RNA, competition hybridization demonstrated that approximately 78% of the enlarged pool of the late 3049 polyadenylated RNA and 72% of the late 1pS pool consisted of sequences unique to the later period. No significant difference in the rate of decay of 3049 and 1pS-specific late polyadenylated RNA was found following actinomycin D block. Infection by either strain of polyoma virus did not alter the rate of decay of total polyadenylated RNA. The hypothesis that the higher levels of 3049-polyadenylated RNA result from enhanced production rather than from increased stability of virus-specific RNA is supported. Furthermore, infection with polyoma virus does not significantly alter the rate of decay of whole-cell polyadenylated RNA. The results indicate that this system may provide a means to study the process of degradation of a relatively limited population of messenger RNA molecules.

- 6859 PHYSICAL MAP OF POLYOMA VIRAL DNA FRAGMENTS PRODUCED BY CLEAVAGE WITH A RESTRICTION ENZYME FROM *HAEMOPHILUS AEGYPTIUS*, ENDONUCLEASE R-HAEIII. (Eng.) Summers, J. (Inst. for Cancer Res., Fox Chase Cancer Center, Philadelphia, Pa. 19111). *J. Virol.* 15(4):946-953; 1975.

32 P-labeled polyoma viral DNA was specifically cleaved with the restriction enzyme of *Haemophilus aegyptius*, endonuclease R-HaeIII, and the physical order on the genome of about 20 of the 22 fragments was identified. The digested DNA was fractionated by electrophoresis on polyacrylamide gels, and the bands were determined by autoradiography. The physical order of the fragments on the polyoma genome was determined by annealing of the denatured isolated fragments to single-stranded circular polyoma DNA. The 3' OH group of the fragment was utilized as a primer for repair type DNA synthesis by DNA polymerase I, directed by the single-stranded circular template. [32 P]TTP and cold dATP, cCTP, and dGTP were used as substrates for the polymerase to label the nucleotide sequences adjacent to the priming fragments. After a short extension of the priming fragment, the remaining template was completed with unlabeled deoxynucleoside triphosphates with the addition of degraded calf thymus DNA primer and a 2,000-fold excess of cold TTP. The final product of this reaction was component II polyoma DNA, in which short regions adjacent to the priming fragment were labeled with [32 P]TTP. Labeled component II DNA from each reaction was sedimented through a neutral sucrose gradient, and the physical order of the fragments was determined by electrophoresis and autoradiography. The autoradiogram was interpreted to construct a physical map of the HaeIII fragments of polyoma

viral DNA. The 5' to 3' orientation of the (+) and (-) strands of the polyoma DNA was determined based on the direction, with respect to the fragment order, in which the (-) strand was elongated. The 5' and 3' direction of the (-) strand was shown to be counterclockwise, while the direction of the (+) strand was clockwise. The described technique for specific radiolabeling of adjacent fragments may be useful for ordering the fragments produced by the digestion of complex DNAs.

6860 REPLICATION OF POLYOMA DNA IN ISOLATED NUCLEI. V. COMPLEMENTATION OF *IN VITRO* DNA REPLICATION. (Eng.) Otto, B. (Med. Nobel Inst., Stockholm, Sweden); Reichard, P. *J. Virol.* 15 (2): 259-267; 1975.

The effect of cytoplasmic extracts of purified enzymes on the synthesis of a viral DNA in isolated cell nuclei was investigated. Prelabeled, depleted nuclei (13 µg DNA) were incubated either in the absence or presence of 20 µl or 50 µl cytoplasmic protein extract from polyoma-infected 3T6 cells. A 50 µl amount of extract was also incubated without nuclei. All incubations were for 30 min under standard conditions with [³²P]dGTP. Nuclei from polyoma-infected 3T6 fibroblasts elongated the progeny strands of the replicative intermediates of polyoma DNA *in vitro*. When the high concentrations of such nuclei were incubated, short DNA fragments were formed and subsequently added onto growing progeny strands. When nuclei were repeatedly washed with buffer containing detergent and then incubated at low concentrations, DNA synthesis was decreased. In particular, the joining process was reduced, resulting in an accumulation of short DNA fragments. All aspects of the synthetic capacity of the nuclei were restored by addition of cytoplasmic extract. Prelabeled, depleted nuclei (13 µg DNA) were incubated without added enzymes; with *Escherichia coli* DNA polymerase I in the presence of either calf thymus DNA ligase I or *E. coli* polynucleotide ligase. Incubations were for 30 min. The standard incubation mixture with [³²P]dGTP was supplemented with NAD⁺ (10⁻⁵ M). Portions of hirt supernatant fluid together with 5 µl of ¹⁴C-labeled linear polyoma DNA as a marker were centrifuged through alkaline sucrose gradients. Additions of the purified enzymes (polynucleotide ligase from calf thymus or *E. coli* together with *E. coli* DNA polymerase I) increased the joining function of the nuclei. The permeability of the nuclear *in vitro* system for proteins appears promising and it seems experimentally feasible to identify enzymes participating in the intermediate steps of DNA synthesis either by fractionation of cytoplasmic extracts or by immunological techniques.

6861 TRANSFORMATION BY POLYOMA VIRUS ALTERS EXPRESSION OF A CELL MUTATION AFFECTING CYCLE TRAVERSE. (Eng.) Burstin, S. J. (New York Univ. Sch. of Medicine, New York, N.Y. 10016); Basilico, C. *Proc. Natl. Acad. Sci. USA* 72(7):2540-2544; 1975.

A temperature-sensitive mutant of baby hamster kidney (BHK) 21/13 cells, tsAF8, which at 39 C were arrested in the G1 (G0) phase of the cell cycle,

were phenotypically altered after transformation with polyoma virus. Polyoma transformation did not produce reversion to a non-temperature-sensitive phenotype but did cause increased entry into S and increased rate of cell death at the nonpermissive temperature (39-39.5 C), compared to untransformed tsAF8 cells. The frequency of cells synthesizing DNA was increased but most of the polyoma-transformed tsAF8 cells that synthesize DNA at the nonpermissive temperature did not divide. At the permissive temperature (33 C), polyoma-transformed tsAF8 cells, unlike tsAF8, also lost viability when exposed to other methods of arresting cells in G1. This study indicates that polyoma viral transformation interferes with the cellular response to this mutation.

6862 RAT CELL LINE 3Y1 AND ITS VIROGENIC POLYOMA- AND SV40-TRANSFORMED DERIVATIVES. (Eng.) Kimura, G. (Tottori Univ. Sch. Med., Yonago, Japan); Itagaki, A.; Summers, J. *Int. J. Cancer* 15(4):694-706; 1975.

The establishment of a rat cell line 3Y1 and its clonal subline, which has a regulated growth property and can be transformed by polyoma virus and simian virus 40 (SV40), is described. The cells were cultured on Dulbecco and Vogt's modification of Eagle's medium. Every three days, cells were trypsinized and transferred to dishes. The medium was changed 6-10 hr after plating to remove residual trypsin and unattached cells. Growing cultures of cells (1x10⁵ to 4x10⁵ cells/dish) were infected with 0.5 ml virus diluted in medium. After 10-14 days, the 10% formalin-fixed cultures were stained, and transformation frequency was determined by counting the deeply stained multilayer colonies. Cell fusion was carried out between SV40-transformed 3Y1 cells and African green monkey kidney (CV-1) cells and between polyoma-transformed 3Y1 cells and BALB 3T3 or C3H2K cells. Wild type viruses were then incubated at 37C, and temperature-sensitive mutants were incubated at 33C. No detectable cytopathic effect of SV40 or polyoma virus was observed, with no decrease in cloning efficiency. SV40 and polyoma viruses initiated an abortive infection in most of the infected 3Y1 cultures; this was in contrast to 3Y1-B clone 1-6 cells. In the transformation studies, the dose-response curve was linear, and characteristic of a single-hit response to the virus. Most of the transformed lines were transformed by the infectious polyoma virion, but not by the defective virion. None of the 17 randomly isolated transformed lines were found to contain infectious SV40 when an extract of 10⁶ cells from each line were tested by the direct plaque assay. The cultures of some lines spontaneously produced a small amount of polyoma virus after prolonged cultivation. In 3Y1-B clone 1 cells, transformation by SV40 and polyoma virus can be assayed with efficiencies comparable to those in the previously available systems for each virus. This cell clone can be transformed by human adenovirus type 12, and should be useful for comparative studies of transformation.

6863 HELPER SPECIFICITY FOR RETRIEVAL OF DEFECTIVE FRIEND VIRUS. (Eng.) Fieldsteel, A. H. (Life Sci. Div., Stanford Res. Inst., Menlo

Park, Calif.); Kurahara, C.; Dawson, P. J. *Int. J. Cancer* 15(3):522-527; 1975.

The extent of helper activity for retrieval of defective Friend virus (FV) was investigated to determine if it was limited to the Friend-Moloney-Rauscher (FMR) group of viruses. Lymphatic leukemia virus (LLV) strains LLV-F (Sw), LLV-F (St), LLV-F (Ha), LLV-R, B/T-LV, AKR and GsLV were tested for their ability to retrieve the FV genome from FV-induced reticulum cell sarcoma (FVTCT) cells. In the *in vivo* system, newborn mice (C3H, BALB/c) were inoculated ip with 0.05 to 0.1 ml of the helper virus, followed 1-28 days later with sc inoculation of 10^5 to 10^6 cells of the syngeneic FVTCT. When the tumor was 1-2 cm in diameter, it was removed, made into a cell free extract and inoculated ip into newborn mice. If retrieval occurred, and a pseudotype had been produced, Friend disease developed in the mice. The *in vitro* system required co-cultivation of the virus-free tumor with a culture actively replicating the helper virus. All three strains of LLV-F were capable of retrieving FV. Both AKR and GsLV failed. All mice inoculated with fluids from co-cultivation of FVTCT with LLV-F (Sw) developed advanced Friend disease in only 31 days, while control mice inoculated only with the LLV (Sw) had not developed lymphatic leukemia when killed 151 days later. FV was not retrieved *in vitro* when embryonic cultures of F₁ hybrids (male AKR x female BALB/c) were co-cultured with FVTCT cultures. GsLV failed to act as helper for FV under *in vivo* conditions, although cell-free extracts of all seven tumors tested yielded GsLV. LLV-R acted as helper, and B/T-LV was as efficient in retrieving FV as any other member of the FMR group of viruses. B/T-LV and LLV-R, as well as both N- and NB-tropic strains of LLV-F function as helper viruses for defective FV. GsLV and AKR viruses do not show helper activity in the test system employed, which, if correct, is in sharp contrast to the MSV strain in which members of both the Gross/AKR and FMR groups of viruses were previously reported to function equally effectively as helpers. The data strongly suggest that only members of the FMR group of viruses can act as helpers for defective FV.

- 6864 DETECTION OF ONCORNAVIRUS ANTIGENIC ACTIVITY IN HUMAN UROTHELIAL TISSUES. (Eng.) Mickey, D. D. (Duke Univ. Med. Cent., Durham, N.C.); Seal, E., Jr.; Paulson, D. F. *J. Urol.* 113(5):658-662; 1975.

Primary malignant, metastatic malignant, and nonmalignant human urothelial tissues were examined by radioimmunoassay to detect protein components which compete with the interspecies antigens of C-type RNA viruses for feline (Rickard) and murine (Friend) oncornavirus antibody binding sites. Following culture in RPMI 1640 containing 20% inactivated calf serum and antibiotics in humidified air with 5% CO₂ at 37 C, tissue explants were homogenized and antigens extracted. Interspecies and species-specific antigens were isolated from feline and murine virus by passage through guanidine gel filtration columns. Monospecific antisera against these antigens were then raised in rabbits. Antigens, labeled with ¹²⁵I via a modified chloramine

T method, and unlabeled tissue extracts were incubated with antisera. Of 68 tissues, 22% showed over 30% (average 50%) decrease in labeled antigen in the precipitate, indicating competition for the feline interspecies antigen. These included three transitional cell bladder carcinomas, one transitional cell renal pelvis carcinoma, five prostatic carcinoma, four benign prostatic hypertrophies, one nontumor bladder tissue and one nontumor kidney tissue. Some tissues showed competition with both feline and murine antigens, while others were competitive in either one. Some extracts showing competition were retested after exposure to sera from patients with urothelial tumors and, again, showed competition. There was thus no globulin population in the patient sera against the competitive tissue extract proteins. None of the extracts showed competition against any species-specific murine or feline leukemia viruses, indicating that the radioimmunoassays were not detecting feline or murine C-type virus. The results suggest either the association of C-type viruses within the tissues showing competitive proteins or the presence of a protein so similar to the interspecies antigen that it cross-reacts.

- 6865 CELL-SURFACE ANTIGENS INDUCED BY FRIEND AND RAUSCHER VIRUS COMPLEXES AND THEIR ASSOCIATED LYMPHATIC LEUKEMIA VIRUSES IN THE RAT. (Eng.) Kuzumaki, N. (Hokkaido Univ. Sch. of Medicine, Sapporo, 060, Japan); Kobayashi, H. *Cancer Res.* 35(7):1718-1722; 1975.

Transplantation experiments and cytotoxicity tests were used to determine the antigenic relationships between the WKA/Mk rat tumors induced by the Friend virus complex, Rauscher virus complex, and by their associated lymphatic leukemia viruses. In the tumor transplantation tests, young adult WKA/Mk rats that had been given ip and sc injections of tumor at birth and had not yet developed primary lymphomas were inoculated sc with cells from each tumor line and observed for tumor growth. Age-matched normal controls were also injected sc with tumor cells. The transplantation studies demonstrated that Friend lymphatic leukemia virus-induced tumors lacked part of the tumor-associated transplantation antigens (TATAs) on the Friend virus complex-induced tumors, and that the former did not express the type-specific (Friend) TATA for the latter not shared by Rauscher virus complex-induced tumors. In contrast, antigenic differences between the TATAs of the Rauscher virus complex-induced tumors and those of Rauscher lymphatic leukemia virus-induced tumors were not clearly demonstrated. Furthermore, the Rauscher lymphatic leukemia-virus-induced tumors had a weak type-specific TATA not shared by the tumors induced by Friend lymphatic leukemia virus.

- 6866 THE CELL-FREE TRANSLATION OF RAUSCHER LEUKEMIA VIRUS RNA INTO HIGH MOLECULAR WEIGHT POLYPEPTIDES. (Eng.) Naso, R. B. (M.D. Anderson Hosp. Tumor Inst., Houston, Tex.); Arcement, L. J.; Wood, T. G.; Saunders, T. E.; Arlinghaus, R. B. *Biochim Biophys Acta* 383(2):195-206; 1975.

Stimulation of cell-free amino acid incorporation and

protein synthesis in Rauscher leukemia virus (RLV) 65S RNA, 35S mengovirus RNA, and reticulocyte A-rich RNA (isolated on oligo (dt)-cellulose columns; not further identified) was investigated. An S30, cell-free amino acid incorporation system, capable of transplanting added 65S RLV RNA was developed from RLV-infected mouse spleen thymus cells. Characteristics in response to RLV RNA included enhanced incorporation upon addition of 65S RLV RNA, and optimal stimulation at 100 mM K⁺ and 3.0 mM Mg²⁺. Amino acid incorporation of the S30 cell-free system appeared to be stimulated equally well by various exogenous messenger RNAs, including RLV RNA, mengovirus RNA, and reticulocyte A-rich RNA under standard conditions. Addition of ribosomal RNA derived from the RLV-infected mouse spleen thymus cells did not result in a stimulation. Analysis of the ¹⁴C-labeled polypeptides made in the S30 system in response to reticulocyte A-rich RNA-directed protein synthesis revealed no stimulation of amino acid incorporation over endogenous synthesis in any polypeptides larger than molecular weight 15,000-16,000; these polypeptides are thus globin-like. Of the stimulated protein products, only those synthesized in response to added RLV RNA were immune-precipitable with anti-RLV rabbit serum, indicating specificity of the antiserum. Analysis of the product of RLV-RNA-directed protein synthesis revealed large polypeptides of 140,000-180,000 molecular weight, plus a range of polypeptides of 50,000-75,000 molecular weight, all of which are immune-precipitated. No polypeptides corresponding to the internal structural polypeptides of mature virions, of molecular weight 11,000-13,000, were induced or synthesized in response to the RLV RNA. These results suggest that the RLV RNA is translated as a polycistronic message with a single initiation site into large molecular weight precursor polyproteins, which are then specifically cleaved *in vivo* into smaller mature viral proteins.

- 6867 ON THE STIMULATION OF VIRAL DNA POLYMERASE ACTIVITY BY NONIONIC DETERGENT. (Eng.) Wu, A. M. (Litton Bionetics, Inc., Bethesda, Md.); Cetta, A. *Biochemistry* 14(4):789-795; 1975.

Mechanisms of the enhancement of DNA polymerase activities by nonionic detergents were studied, with particular interest in the roles of template-primer, specific stimulation, and detergent enzyme stabilization. R-murine leukemia virus and murine sarcoma virus reverse transcriptase were purified and employed. In assaying DNA polymerase activity, reactions were stopped by the addition of ice cold 10% trichloroacetic acid containing 0.02 M sodium pyrophosphate; the acid precipitable radioactivity was then determined. RNA-directed DNA synthesis was stimulated by a relatively low concentration of Triton X-100, a 0.02% detergent yielding 5-fold stimulation; many other non-ionic detergents illustrated similar stimulatory activity. Use of purified enzymes precluded stimulation due to an inhibition of nuclease activity. In addition, a nonspecific protective effect in the stimulation of enzyme activity was delegated a minor role. The stimulatory effect of Triton X-100 was dependent on the template primer. DNA synthesis was most highly stimulated with (dT)_{12-18x} (rA)_n and SSa; minimal

stimulation was with (dT)_{12-18x}(dA)_n or DOS viral RNA. Such stimulation was found in reverse transcriptase from avian, mouse and primate type-C virus; in the cytoplasmic pellet fraction of human leukemic WBC; but not in DNA polymerase purified from prokaryotes or from human cells. There was a narrow range of 0.015-0.005% Triton X-100 concentration for maximal endogenous DNA polymerase activity from detergent disrupted viruses, with higher concentrations being inhibitory. In the absence of Triton X-100, DNA synthesis reached a maximum at 20 µg/ml (dT)_{12-18x} · (rA)_n; in the presence of the detergents, the rate of synthesis increased up to a concentration of 200 µg/ml. This observation is suggested to be due to the prevention of (rA)_n collapse. In analyzing the kinetics of DNA synthesis in the presence and absence of Triton X-100, it was shown that the non-ionic detergent enhances the rate of synthesis, both early and late after initiation of (dT)_n synthesis. In addition, thermal inactivation of viral DNA polymerases was partially overcome by the presence of nonionic detergent. These factors may be used in distinguishing the viral enzyme from most cellular DNA polymerases.

- 6868 INHIBITION OF RNA-DEPENDENT DNA POLYMERASE OF MURINE ONCORNAVIRUSES BY AMMONIUM-5-TUNGSTO-2-ANTIMONIATE. (Eng.) Chermann, J. -C. (Unite d'Oncologie Virale, Departement de Virologie, Institut Pasteur, 28, rue du Dr. Roux, 75015 - Paris, France); Sinoussi, F. C.; Jamin, C. *Biochem. Biophys. Res. Commun.* 65(4):1229-1236; 1975.

To elucidate the mode of action of ammonium 5-tungsto-2-antimoniate (TA), its action on the reaction catalyzed by RNA dependent DNA polymerase from murine leukemia virus (MLV, Moloney isolate) was studied. TA invariably inhibited the activity of MLV RNA dependent DNA polymerase as stimulated by various synthetic template-primers. Fifty percent inhibition of the poly(A) oligo(dT) stimulated DNA polymerase was obtained with a concentration of 1.25 µg/ml, whereas inhibition of the poly(C) poly(dG) stimulated activity was achieved with a concentration of 6 µg/ml. The inhibition was reversible and competitive for template-primer. The strongest inhibition was achieved when TA was pre-incubated for 15 min at 37 C with the enzyme. *Escherichia coli* RNA polymerase and DNA polymerase were also strongly inhibited by TA. The results suggest that TA acts at the binding site of the enzyme for template-primary, that TA inhibition can not be attributed to a polyanion-like effect, and that the inhibition by TA is highly specific for the polymerases. The effect of TA *in vivo* may be primarily due to a selective action upon the enzymatic polymerization step.

- 6869 AN *IN VITRO* FOCUS-INDUCTION ASSAY FOR XENOTROPIC MURINE LEUKEMIA VIRUS, FELINE LEUKEMIA VIRUS C, AND THE FELINE-PRIMATE VIRUSES RD-114/CCC/M-7. (Eng.) Peebles, P. T. (Nat'l. Cancer Inst., Bethesda, Md. 20014). *Virology* 67(1): 288-291; 1975.

A rapid focus-induction assay was developed for cer-

tain replicating (r+) but nontransforming (t-) mammalian type C viruses including: xenotropic murine leukemia virus, feline leukemia virus type C, and feline-primate viruses RD-114 and CC3AV. Mink cells infected only with r-t+ defective Moloney murine sarcoma virus were introduced into a phenotypically flat cell line (S+L- MiCl₁). Superinfection of S+L- MiCl₁ monolayers with dilutions of the r-t+ type C viruses resulted in focus formation occurring with one-hit kinetics. Pretreatment of the cells with either DEAE-dextran or polybrene enhanced focus induction. Quantitation of r-t+ virus by use of S+L- MiCl₁ cells may possibly prove useful for direct neutralization of the compatible r-t+ viruses. Heterologous S+L- MiCl₁ host cells should also provide a means for either cloning the compatible r-t+ viruses or studying their genetic interaction with the clones of murine sarcoma virus present.

- 6870 VIRUSES IN OSTEOSARCOMAS INDUCED BY ²²⁶Ra: A STUDY OF THE INDUCTION OF BONE TUMOURS IN MICE. (Eng.) Lloyd, E. L. (Radiological and Environmental Res. Div., Argonne Natl. Lab., Argonne, Ill. 60439); Loutit, J. F.; Mackevicius, F. *Int. J. Radiat. Biol.* 28(1):13-33; 1975.

Experiments were carried out to determine if a virus is involved in the production of bone tumors, if sex affects the incidence of bone tumors, and if one strain of mice is more likely to develop osteosarcoma. Male C3H/H mice, female C3H/H mice, and female CBA/H mice, divided into three groups of 15 animals each, were injected ip with 0.5 μ Ci ²²⁶Ra (a dose previously shown to be associated with a high incidence of osteosarcoma). Osteosarcomas developed in 14 of the female C3H/H mice (animals known to carry mammary tumor viruses in milk) but in only six of their 15 male counterparts. Among uninjected C3H/H controls, only one male and no females developed osteosarcoma. Mammary tumors occurred in nine of the experimental females and in ten of the control females. In the CBA/H mice, which have a very low incidence of mammary tumors and leukemia, seven of the 15 injected females developed osteosarcoma. No osteosarcomas were observed in the controls, and no mammary tumors occurred in either the injected or control groups. The CBA/H mice lived about 5-8 mo longer than C3H/H mice, and their osteosarcomas appeared at a correspondingly later date. Virus particles were detected in each of the three mammary tumors and in 15 of the 17 osteosarcomas examined by electron microscopy. It cannot be concluded that osteosarcomas are caused by a virus; however, the results suggest that viruses may at least contribute to the development of osteosarcomas in mice.

- 6871 MAMMARY TUMOR VIRUS INDUCTION BY GLUCOCORTICOIDS. CHARACTERIZATION OF SPECIFIC TRANSCRIPTIONAL REGULATION. (Eng.) Parks, W. P. (Natl. Cancer Inst., Bethesda, Md.); Ransom, J. C.; Young, H. A.; Scolnick, E. M. *J. Biol. Chem.* 250(9):3330-3336; 1975.

A study of the physiologic conditions and characterization of *in vitro* stimulation of murine mammary tumor virus by dexamethasone was undertaken to determine the specificity and mechanisms of in-

duction in terms of the biological parameters of glucocorticoid stimulation of murine mammary tumor virus. Dexamethasone (1,4-pregnadiene-9-fluor-16 α -methyl-11 β ,17 α ,21-triol-3,20-dione), stimulated mouse mammary tumor virus expression 10- to 20-fold in C3H MT cl 6 tissue culture cells. This hormone effect was observed at concentrations as low as 1×10^{-10} M and was maximal at 10^{-7} - 10^{-8} M. The time course of induction indicated that detectable increases in extracellular viral DNA polymerase were first noted 18-24 hr following the addition of dexamethasone, and cells produced the highest polymerase levels at the time monolayers approached confluence. Steroid responsiveness was associated with specific increases in type B murine mammary tumor virus structural polypeptide (gp52(s1)) expression and murine mammary tumor virus RNA that quantitatively paralleled the increase in extracellular virus production as measured by electron microscopy and supernatant RNA-dependent DNA polymerase activity. Another virally transformed murine cell line, KA 31, did not contain detectable levels of murine mammary tumor virus gp52(s1) or RNA before or after dexamethasone stimulation; thus induction was noted only in murine cells with preexisting murine mammary tumor virus expression. No increase in basal levels of type C murine leukemia viral proteins or RNA was detected in dexamethasone-treated mammary cell lines that were producing increased levels of murine mammary tumor virus. Therefore, increases in murine mammary tumor virus gene products are specific for murine mammary tumor virus DNA sequences under these conditions.

- 6872 ALTERATION OF MALIGNANCY IN CULTURED CELLS. (Eng.) Fischinger, P. J. (Natl. Cancer Inst., Bethesda, Md. 20014); Nomura, S. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 183-188.

The phenomenon of reversion in cells transformed by the Moloney (M) and Kirsten (K) isolates of murine sarcoma virus (MSV) was studied in mouse 3T3 cells, cat CCC cells, human AV3 cells, and mouse BABL/c 3T3 cells. Immediately after transformation with the M1 M-MSV genome, over 50% of the cell clones from a transformed focus were flat and when infected with murine leukemia virus (MuLV) did not yield free M-MSV. Even after several cycles of cloning, the apparent frequency of reversion remained high. With the m3 M-MSV genome, the reversion frequency was generally low, although a ten-fold greater frequency was observed in some subclones. Mouse MSV-transformed cells readily yielded phenotypic and true flat variants, and among the phenotypic revertants, a gradation of morphology from very flat contact-inhibited monolayers to quite dense multilayered cultures was seen. Six true cat cell revertant clones were also isolated, but flat variants were very rare among the human cells and were only phenotypic when they did occur. All true revertants in both cat and mouse cells were flat, contact inhibited,

reached low saturation densities, were often slow growing, and were quite susceptible to infection with various helper viruses but in no case released free MSV. Spontaneous revertants infected with m3 M-MSV showed greater susceptibility to re-infection with M-MSV than parental cells, revertants infected with K-MSV did not differ in susceptibility from the parental BALB/c 3T3 cells, and cat cell revertants were as or less susceptible as compared with the parental cells. Infection of cat and mouse cells by pure ecotropic MuLV yielded endogenous xenotropic virus. Mouse and human cell revertants were positive for MuLV p30 antigen and MuLV glycoprotein (gp) 71, but the cat cells were not. Retransformation of revertant mouse cells with the same MSV genome was possible, the cells showing a temporal variability regarding MSV rescue by actively replicating MuLV. Revertants retransformed by another MSV produced flat variants, but this property was not stable. Revertants infected by K-MSV could be transformed by M-MSV, and MSV was rescued on infection by MuLV, reversion being possible only if the two transforming genomes were molecularly dissimilar. The results indicate that the phenomenon of reversion in MSV-transformed cells is quite complex, both the virus and cell participating in the eventual outcome.

- 6873 INDUCTION OF ERYTHROID LEUKAEMIA BY HARVEY AND KIRSTEN SARCOMA VIRUSES. (Eng.) Scher, C. D. (Harvard Medical Sch., Boston, Mass. 02115); Scolnick, E. M.; Siegler, R. *Nature* 256(5514):225-226; 1975.

Kirsten sarcoma virus (KiSV) and Harvey sarcoma virus (HaSV) were rescued with Moloney leukemia helper virus (MLV-M) and tested for the ability to induce erythroid leukemia in mice. About 10^6 nonproducing cells (lines NIH/3T3, NRK, and BALB/c-3T3) were transferred to a flask containing $4 \mu\text{g ml}^{-1}$ polybrene and infected at 24 hr with 10^7 XC units MLV-M, and then passaged for 2 wk. To prepare virus stock, 10^6 cells were transferred to a flask and tissue culture fluid was collected at 24 hr and stored at -70°C . To induce erythroid leukemia, filtered virus stock (0.1 ml) was inoculated ip in newborn Swiss mice. The animals were killed and autopsied at three to four wk. Spleens were examined for erythroblastic foci. Virus from MLV-M-infected HaSV- or KiSV-transformed nonproducers transformed NIH/3T3 cells and caused leukemia in Swiss, BALB/c, and C57BL/6 newborn mice. Approximately 10^7 transforming units of HaSV or KiSV caused microscopic foci of erythroid leukemia in 50% of the inoculated animals while 10 transforming units did not cause leukemia. Some animals also developed solid tumors (usually rhabdomyosarcomas or fibrosarcomas). At all dilutions that caused disease, the incidence of erythroid leukemia was greater than that of solid tumors. Thus, defective sarcoma viruses rescued with MLV-M can cause erythroid leukemia in mice.

- 6874 TRANSFORMATION OF HORSE SKIN CELLS BY TYPE-C SARCOMA VIRUSES. (Eng.) Rhim, J. S. (Microbiol. Assoc., Inc., Bethesda, Md.);

Ro, H. S.; Kim, E. B.; Gilden, R. V.; Huebner, R. J. *Int. J. Cancer* 15(2):171-179; 1975.

The transformation of horse skin cells *in vitro* by the Kirsten murine sarcoma virus (Ki-MSV) and MSV pseudotype with woolly monkey type C virus was reported. The ST strain of the feline sarcoma virus (FSV-ST) and MSV pseudotypes with gibbon monkey, RD-114 AT-124, baboon placenta, Murine xenotropic (BABL/c3T3 and C57L/JD) type C virus transformation of horse skin cells was also studied. The horse skin [E. Derm, NBL-6(CCL-57), passage 15] line was derived from the dermis of a four-year old quarter-horse mare. The passage 18- through 28-level was used. Virus replication was determined by examination for the presence of morphological alterations, assay for the complement-fixing (CF) antigen reactive with respective type C leukemia virus group-specific (gs) antiserum and assay for RNA-dependent DNA polymerase activity. At 4-5 days after KiMSV and MSV-simian sarcoma-associated virus (MSV-SSAV) infection, foci consisting of fusiform cells mixed with round cells appeared in infected cultures. The foci gradually increased in size and showed a pronounced proliferative effect with multilayered cell growth. Multinucleated giant cells were characteristic of MSV-SSAV-infected cultures. Degeneration in the central areas of transformed foci appeared at 10-14 days, and by day 18 the clear plaques were stained and countable. Cell-free preparations of supernatant fluid from transformed cultures produced similarly altered foci in Fischer rat embryo and horse skin cells, but not in NIH Swiss mouse embryo cells. Transformed cells contained gs antigens of their respective type C leukemia virus. KiMSV-transformed cell suspensions were CF-positive for murine leukemia virus gs antigen and negative for rat and woolly leukemia virus gs antigen, while MSV-SSAV-transformed cell suspensions were positive only for woolly leukemia virus gs antigen. Clones of transformed cell foci continued to show altered morphology and contained high titers of gs antigens and reverse transcriptase activity. Foci formation by KiMSV stock virus from a normal rat kidney carrier line was almost equally efficient in normal rat kidney, NIH Swiss mouse embryo and horse skin cells. Only the Moloney and Harvey MSV viruses did not induce transformation of horse skin cells. These results indicate that horse skin cells are useful for transformation assay of type C sarcoma viruses of both exo- and xenotropic origin.

- 6875 CYCLIC AMP-MEDIATED TRANSFORMATION OF RAT CELLS TRANSFORMED BY TEMPERATURE-SENSITIVE MOUSE SARCOMA VIRUS. (Eng.) Somers, K. D. (Eastern Virginia Medical Sch., Norfolk, Va. 23507); Rachmeler, M.; Christensen, M. *Nature* 257(5521):58-59; 1975.

To examine the relationship between the level of adenosine 3',5'-cyclic AMP (cAMP) and the expression of transformed phenotype by virus-transformed cells, three cell lines were studied: normal rat kidney cells (NRK); NRK cells transformed by Moloney sarcoma-leukemia virus [NRK(MSV-MLV)]; and NRK cells transformed by a cold-sensitive mutant

of MSV [NRK(MSV-1b)]. After a ten-minute exposure at 33 C to 0.04 mM 8-bromo-cyclic AMP (8-Br-cyclic AMP), morphological change was noted in NRK(MSV-1b) cells, that reached maximum expression by one hour. The effect was to change the phenotype from that present at the nonpermissive temperature of 33 C (cells flattened and poorly refractile) to that characteristic of cells grown at 39 C, the permissive temperature (cells rounded, highly refractile). When using 0.4 mM N⁶,O^{2'}-dibutyryl cyclic AMP (db-cyclic AMP) plus theophylline at 33 C, changes were apparent after three hours and maximized by 24 hr. In both cases, 100% of the cells changed, and remained altered as long as the additive was present, up to 72 hr. Removal of the cyclic AMP analogues resulted in a rapid reversal (within one hour) from the transformed to the normal phenotype. Changes were independent of growth phase. The addition of cyclic AMP analogues to uninfected NRK cells and transformed NRK(MSV-MVL) cells provoked no change, regardless of temperature (33, 36, or 39 C). Cyclic GMP and other cyclic nucleotides produced no change in NRK(MSV-1b) cells. Levels of cyclic AMP measured by radioimmunoassay were three times as high at permissive as at nonpermissive temperatures. Temperature shifts produced marked changes: levels increased approximately three-fold within five hours after a shift from nonpermissive to permissive temperatures; in shift-down experiments, levels fell 50% within 24 hr. Under similar conditions, no significant differences for NRK or transformed NRK(MSV-MLV) cells were found. It is concluded that this system is an important exception to mechanisms proposed for the role of cyclic AMP in the expression of the transformed state, which postulate decreased cyclic AMP levels for transformed cells.

- 6876 TWO LEVELS OF RESTRICTION BY MOUSE OR CAT CELLS OF MURINE SARCOMA VIRUS COATED BY ENDOGENOUS XENOTROPIC ONCORNAVIRUS. (Eng.) Fischinger, P. J. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Nomura, S.; Blevins, C. S.; Bolognesi, D. P. *J. Gen. Virol.* 29(1):51-62; 1975.

Mouse and cat cells were each examined for the mode of restriction of endogenous xenotropic oncornavirus. The mouse cell lines included normal Swiss 3T3FL, inbred BALB/c 3T3, and wild mouse-derived SC-I cells. Murine xenotropic helper virus (MuX) and its pseudotype of Moloney murine sarcoma virus (MSV(MuX)) were grown in cat cells (feline embryo fibroblasts) to high titer. MuX alone did not replicate in any mouse cell tested including normal or transformed outbred Swiss 3T3 cells or SC-1 cells, but did grow in cat cells, human embryonic muscle skin cells, and in normal rat kidney cells. MSV-(MuX) was not able to achieve that intracellular state from which it could be rescued by mouse leukemia virus (MuLV) in any mouse cell tested with the exception of SC-1 cells. Sequential passage of MSF(MuX) virus complex in SC-1 cells resulted in a loss of infectious sarcoma and helper viruses; but transformed, MSV rescuable cells were retained. If cat embryo cells were infected with either the feline endogenous xenotropic virus (FeX) or its MSV pseudotype (MSV(FeX)), two analogous states

of restriction were observed. FeX alone did not replicate in cat cells as measured by release of progeny virus or by FeX group-specific antigen induction. Cat cells could be susceptible or insusceptible to the entry of MSV(FeX) as measured by MSV rescue with appropriate ecotropic feline leukemia virus. A single strain of cat cells became very insusceptible to MSV(FeX) on prolonged passage. Two levels of cellular restriction can be distinguished in each of two mammalian cell systems by the susceptibility to penetration of MSV coated with endogenous xenotropic oncornavirus.

- 6877 LOW FREQUENCY OF (5'-3') -C-G- CONNECTION IN 70S RNA FROM SIMIAN SARCOMA VIRUS. (Eng.) Ohe, K. (Faculty Medicine, Hiroshima Univ., Kasumi-cho, Hiroshima, Japan); Oppenheim, L. B. *J. Virol.* 16(3):729-735; 1975.

The molar frequency of oligonucleotides obtained from simian sarcoma virus 70S RNA by guanidic acid-specific cleavage was compared with the frequency expected of an RNA molecule in which nucleotides are arranged in random distribution. Approximately 5×10^8 KW23 cells (normal rat kidney cells transformed by simian sarcoma virus) were incubated overnight with 75 mCi [³²P]phosphate. ³²P-labeled 70S RNA was obtained from purified virus by centrifugation, digested directly with RNase T₁, fractionated by electrophoresis and homochromatography and further purified by electrophoresis on DEAE-cellulose. The internal sequence of the oligonucleotides was analyzed by degradation with 0.4 mg RNase A/ml. The ratio of the parent oligonucleotides was calculated from the molar yield of fragments, allowing a small counting error for mononucleotides Cp and Gp. The number of counts originally derived from each pure oligonucleotide, which is proportional to its molar frequency, was calculated. The frequency of C-Gp-containing oligonucleotides of simian sarcoma virus 70S RNA was markedly lower and that of A-Gp-containing oligonucleotides was higher than expected by random distribution. This deviation from randomness was similar to the deviation of nearest neighbor frequency of DNA from mammalian cells and DNA-containing tumor viruses. The authors suggest that the nucleic acids of tumor viruses, whether DNA or RNA, share the same general characteristic as the DNA of mammalian cells, that is, a low frequency of -cytosine-guanosine-connection.

- 6878 STABILITY OF SIMIAN VIRUS 40 (SV40) mRNA SPECIES. (Eng.) Ho, L. (University College Hospital Medical Sch., University St., London WC1E 6JJ, England); Cohen, A. *Virology* 67(2):588-590; 1975.

The stability of early and late simian virus 40 (SV40) messenger RNA (mRNA) was compared in CV-1 cells infected with SV40 at a multiplicity of 100 plaque-forming U/cell. For the study of early mRNA, virus-infected cells were labeled with ³H-uridine in the presence of cytosine arabinoside. After 24 hr, RNA was extracted from polysomes, hybridized to SV40-DNA, and eluted before analysis by centrifugation in a linear sodium deodecyl sulfate-sucrose gradient. For the study of late SV40 mRNA, infected

cells were labeled with ^3H -uridine for ten hours only after the 24-hr cytosine arabinoside block was reversed by deoxycytidine. SV40-specific mRNA was extracted and analyzed as above. The only species of early SV40 mRNA obtained was that sedimenting at 19S. This species was stable for 15 hr and was not converted to any other detectable species. In contrast, two species of late SV40 mRNA were obtained which sedimented at 19 and 16S. The late 19S mRNA was much less stable than the early 19S mRNA and was reduced to 40% of its original peak height within five hours. It was also less stable than the late 16S component. Since both late components were present on polysomes, a precursor-product relationship is unlikely. The different stabilities of the virus-specific mRNA species must depend on their functional lifetime, and this may reflect inherent structural differences and play some role in regulating viral protein synthesis.

- 6879 AMINO ACID AND SUGAR TRANSPORT IN CELLS PERMISSIVELY INFECTED WITH SIMIAN VIRUS 40. (Eng.) Miller, M. S. (Central Emergency Hosp., Afula, Israel); Kwock, L.; Wallach, D. F. H. *Cancer Res.* 35(7):1826-1829; 1975.

The transport of α -aminoisobutyric acid (AIB) and 2-deoxy-D-glucose in African green monkey kidney cells (VERO) infected with SV40 was studied. Prior to transport experiments, cells were grown in media containing [^3H]AIB or [^3H]-2-deoxy-D-glucose. Cultures from each experimental group were examined for viral cytopathic effects at 24 hr intervals; by 96 hr, 100% of the cells had rounded up and detached from the coverslips. Initial uptake of AIB did not differ between control and virus-infected cells. A Lineweaver-Burk plot yielded a two-component curve for AIB transport at all times examined, illustrated increased V_{max} for the transformed cells and, hence, indicated two transport systems of differing substrate affinity and multiple uptake modalities. K_m values of 1×10^{-3} to $2.9 \times 10^{-3}\text{M}$ for control cells and 1×10^{-3} to $2.5 \times 10^{-3}\text{M}$ for infected cells were obtained. Likewise, no difference in uptake of 2-deoxy-D-glucose was noted between the virally infected and control cells; the control K_m was 1.5×10^{-3} to 1.8×10^{-3} , while the K_m for infected cells was 1.5×10^{-3} to 2.0×10^{-3} , with no significant change in V_{max} . The data showed that permissive infection of VERO cells with SV40 did not appreciably increase or decrease transport of AIB or 2-deoxy-D-glucose between eight hr after virus infection and cell death. It was thus suggested that enhanced sugar and amino acid transport by SV40-transformed oncogenic cells is a function of the host genome and the transformed state.

- 6880 STIMULATED PHOSPHORYLATION OF NON-HISTONE PHOSPHOPROTEINS IN SV-40 TRANSFORMED WI-38 HUMAN DIPLOID FIBROBLASTS. (Eng.) Pumo, D. E. (Dept. Zool., Univ. Michigan, Ann Arbor); Stein, G. S.; Kleinsmith, L. J. *Biochim. Biophys. Acta* 402(1):125-130; 1975.

Because the phosphorylation of nonhistone proteins

has been suggested to play a role in the regulation of eukaryotic gene transcription, the phosphorylation of these proteins was compared in normal and simian virus 40 (SV40)-transformed WI-38 human diploid fibroblasts. Exponentially growing cells were labeled by incubation for one hr in phosphate-free medium containing 100 mCi/ml $^{32}\text{P}_i$, after which the nuclei were isolated in the presence of the protease inhibitor 1-l-tosylamide-2-phenyl-ethylchloromethyl-ketone (50 mg/ml). The nuclei were homogenized and the phosphorylated nonhistone protein-rich supernatant was electrophoresed in sodium dodecyl sulfate/phosphate acrylamide gels. The nonhistone phosphoprotein fraction prepared from the diploid fibroblasts was highly heterogeneous, with up to 27 bands being routinely resolvable. The composition of this fraction was the same in the normal and SV40-transformed fibroblasts, but there were small quantitative differences in the relative amounts of several protein species. In contrast, there were marked quantitative and qualitative differences in protein phosphorylation. In terms of the rate of phosphorylation, stimulations of between 7- and 13-fold were repeatedly observed in log phase transformed cells pulsed for one hr with ^{32}P compared to normal cells in four separate experiments. Change in the specific activities of the phosphate pool could not account for the enhanced incorporation of ^{32}P into nonhistone proteins, and experiments with cycloheximide indicated that this phosphorylation was occurring in pre-existing protein species. This is the most dramatic alteration in nonhistone protein phosphorylation ever described and may therefore have important implications for understanding malignant transformation.

- 6881 SOME ULTRASTRUCTURAL FEATURES OF THE CELL SURFACE AFTER SV40 TRANSFORMATION AND SOMATIC HYBRIDIZATION WITH NORMAL UNTRANSFORMED CELLS. (Eng.) Kilarski, W. (Wistar Inst. Anatomy and Biology, Philadelphia, Pa. 19104). *Cancer Res.* 35(10):2797-2807; 1975.

Two simian virus 40 (SV40) transformants were studied by the concanavalin A (Con A)-peroxidase method and electron microscopy to determine the extent of the resemblance between hybrid cell coat architecture and that of the parental cell coat. In addition, the ability of the cell surfaces to maintain certain unwashed components that are ruthenium red (RR) positive was correlated with the type of transformation. Skin fibroblasts from a patient with Lesch-Nyhan syndrome that were transformed by SV-40 (LN-SV), normal human fibroblasts, mouse macrophages, and somatic hybrids of mouse macrophages and LN-SV cells were employed. All cell types studied, normal, transformed, and hybrids, expressed a positive surface reaction with Con A-peroxidase; however, the specific surface deposit thickness varied for each type of cell. Normal human fibroblasts had a thicker layer (40 nm) than did the transformants (35 nm), mouse normal macrophages (27 nm), and hybrids (30 nm). At least one-half of the material contributing to the cell surface coat and RR positive reaction was washed away when the cells were rinsed thoroughly with PBS before fixation. In normal human fibroblasts and LN-SV transformants, the region of the surface over the

nucleus was covered unevenly by the reaction product. The ration of Con A binding sites to gaps was 4:1 in the normal human fibroblasts and 3.2:1 in the LN-SV cells. The mouse macrophages also showed an uneven distribution of the Con A reaction product; no differences were observed between the central and the peripheral portions, and the binding site:gap ratio was 1.6:1. The somatic hybrids had surface properties that closely resembled those of the parental cell lines, especially those of the mouse macrophages, but had the lowest binding site:gap ratio of 1:1. In general, in all four cases the central region showed less continuous labeling than the peripheries, while the marginal portions were usually devoid of the reaction product. Thus, normal human fibroblasts had the most continuous surface reaction, and thickest reaction product, and the greatest Con A:gap ratio.

- 6882 PRESENCE OF SIMIAN 40 VIRUS NON-INTEGRATED DNA IN NON-PRODUCTIVE CELLS TRANSFORMED BY THIS VIRUS. (Fre.) Daya-Grosjean, L. (Institut de Recherches Scientifiques sur le Cancer, B. P. no 8, 94800 Villejuif, France); Benichou, D.; Monier, R. *C. R. Acad. Sci. [D] (Paris)* 281(10):679-682; 1975.

The extraction of nucleic acids with hot phenol revealed the existence of small quantities of simian virus 40 (SV40) DNA nonintegrated into the transformed cells of hamster (TSV₅Cl₂) and a mouse (MKS₅V). The TSV₅Cl₂ clone was semipermissive for SV40 but, after confinement, it lost its capacity to spontaneously produce detectable quantities of virions. The MKS₅V strain which came from non-permissive cells was never productive. The infectious element was experimentally determined to be DNA. The small quantities so far obtained suggest the SV40 DNA is circular superhelical (form I) since linear DNA (form III), even added in significant amounts, is hardly recuperable with the hot phenol method. The selectivity of this method is apparently due to the denaturation of the DNA which remains in interphase with the proteins while the RNA passes into the aqueous phase. A DNA of low molecular mass and of circular superhelical conformation is capable of renaturing itself very rapidly since both chains remain intertwined when denatured and are genetically simple. The hot phenol method is more forceful than the Hirt technique; it assures an effective destruction of nucleic structures and thus makes its possible to detect traces of infectious viral DNA which had remained unobserved until then. The presence of infectious viral DNA in nonproductive transformed cells is likely to be explained by the assumption that only a small portion of the cell population contains free viral DNA the existence of which could be due to the sudden excision of the integrated genome, possibly followed by replication. Spontaneous induction in a small number of cells in each generation is well in accord with the observed facts, notably that the cells examined could not be induced to produce virions when exposed to mitomycin, N-methyl-N'-nitro-N-nitrosoguanidine, or to UV radiation.

- 6883 ANTIGENIC DETERMINANTS OF THE 70,000 MOLECULAR WEIGHT GLYCOPROTEIN OF WOOLLY MONKEY TYPE C RNA VIRUS. (Eng.) Hino, S. (Natl. Cancer Inst., Bethesda, Md. 20014); Stephenson, J. R.; Aaronson, S. A. *J. Immunol.* 115(4):922-927; 1975.

The 70,000 molecular wt glycoprotein (gp70) of a type-C RNA virus originally isolated from a woolly monkey was partially purified and immunologically characterized. Evidence that this is a virus-coded protein was derived from studies showing its antigenic properties to be unaltered by virus passage in cells of different species. A broadly reactive competition immunoassay was developed utilizing antiserum prepared against feline leukemia virus to precipitate ¹²⁵I-labeled woolly monkey virus gp70. Gibbon and woolly viruses, as well as feline and several mouse type-C viruses, all reacted with equal efficiency in this assay. In contrast, an endogenous virus of the baboon failed to cross-react, suggesting that viruses of this latter group are less immunologically related to the others. In a homologous competition immunoassay for the woolly viral glycoprotein, the woolly virus was readily distinguished from otherwise closely related viruses of gibbon apes. These findings demonstrate the pronounced type-specific antigenic determinants possessed by this viral protein. The antigenic determinants of gp70 responsible for neutralization were also investigated. Antisera to woolly monkey virus neutralized the infectivity of this virus but had no neutralizing activity for Rauscher leukemia virus (R-MuLV). Antisera to R-MuLV neutralized this virus but not woolly monkey virus. Antisera to feline leukemia virus caused little or no neutralization of woolly monkey virus or R-MuLV. All the antisera precipitated the gp70s of these two viruses, indicating that the antigenic determinants detected by direct precipitation of gp70 are more broadly reactive than the determinants responsible for virus neutralization.

- 6884 DIFFERENTIAL EXPRESSION OF HELPER VIRAL STRUCTURAL POLYPEPTIDES IN CELLS TRANSFORMED BY CLONAL ISOLATES OF WOOLLY MONKEY SARCOMA VIRUS. (Eng.) Aaronson, S. A. (Natl. Cancer Inst., Bethesda, Md. 20014); Stephenson, J. R.; Hino, S.; Tronick, S. R. *J. Virol.* 16(5):1117-1123; 1975.

Normal rat kidney cell lines transformed by woolly monkey sarcoma virus (WSV) in the absence of infectious virus production were analyzed for the expression of woolly monkey helper viral p30, p12, and gp70 antigens. Several lines produced high levels of both p30 and p12, whereas gp70 was not detectable. One transformed clone expressed only p12, and in another cell line, none of the helper viral antigens were detected. The properties of each sarcoma virus bred true upon transmission, indicating that each variant represents a distinct genotype. The different cell lines were examined with respect to properties characteristic of the transformed state. The *in vitro* growth properties and oncogenicity of each WSV-transformed clone were indistinguishable, indicating that their capacities to induce helper viral antigens have little relationship with their transformation abilities.

- 6885 THE ONCORNAVIRUS GLYCOPROTEIN gp69/71: A CONSTITUENT OF THE SURFACE OF NORMAL AND MALIGNANT THYMOCYTES. (Eng.) Del Villano, B. C. (Scripps Clin. Res. Found., La Jolla, Calif.); Nave, B.; Croker, B. P.; Lerner, R. A.; Dixon, F. J. *J. Exp. Med.* 141(1):172-187; 1975.

Three oncornavirus-related proteins associated with the surface of normal and malignant thymocytes were studied; these included virion-associated proteins, gp 69/71, p45, and p30. Experimental animals employed included mouse strains and hybrids BALB/c, (BALB/c x NZB)F₁, C3H/St, C57BL/6J, Nu/nu, nu/nu, NZB, NZW, (NZB x NZW)F₁. Rat anti-Moloney leukemia virus (MLV) was obtained from Fisher rats immunized with syngeneic tumor cells induced by MLV. In characterizing rat anti-MLV, reactivity was determined by indirect immune precipitation using four kinds of radioiodinated antigen preparations; of the three classes of labeled proteins from disrupted Scripps leukemia virus, (SLV), gp69/71, p45, and p30, the principle antigen reacting with rat anti-MLV was gp69/71. Tumor cells from 34 involved thymuses, 31 involved spleens, and three involved lymph nodes of mice with Murine leukemia virus-induced lymphomas were analyzed to characterize virus-related cell surface antigens. Histological examination demonstrated the replacement of essentially all normal cells by malignant cells classified as either lymphocytic lymphomas or as reticulum cell sarcomas, with no antigenic differences between lymphomas induced by SLV and MLV. Variation in the molecular size of virus-associated proteins present in different tumors was observed and confirmed by electrophoresis in polyacrylamide gradient slab gels. Testing by indirect immune precipitation followed by polyacrylamide gel electrophoresis revealed antibodies against gp69/71 in sera of 29% of mice infected with SLV at birth, but in none of the 28 uninfected mice. Indirect immune precipitates revealed the presence of antibody to their own lymphoma cell surface antigens in two MLV-infected mice. The significance of the restricted presence of antigens coded for by the viral genomes to the surface of some differentiated cells is discussed in reference to the relationship between leukemia-associated, differentiation-dependent, and virion markers and the possible consequence to the host.

- 6886 QUANTITATION OF RNA TUMOR VIRUSES BY SPECTROSCOPY OF DENSITY GRADIENT GELS. (Eng.) Liebes, L. F. (Michigan Cancer Foundation, Detroit, Mich. 48201); Retzel, E. F.; Maher, V. M.; Rich, M. A.; McCormick, J. J.; Salmeen, I.; Rimai, L. *J. Virol.* 16(3):546-552; 1975.

A system was developed for virus particle quantitation based on the measurement of the optical absorbance of stained viruses. These viruses were first banded at their buoyant density in an equilibrium 24-53% (wt/wt) sucrose density gradient, then fixed in position in the gradient by photopolymerizing an acrylamide-riboflavin mixture in the sucrose, and finally stained and destained. Using plasma from mice infected with Rauscher leukemia virus or chickens infected with avian myeloblastosis virus (BAI strain) or suitable controls, it was shown that this technique specifically detects RNA tumor viruses.

By using virus stock solutions for which the absolute concentrations were determined by laser beat frequency spectroscopy, the absorbance of the viral bands was calibrated in terms of virus particle concentration. Using 0.8-ml gradient gels (4 x 45 mm) as low as 2×10^7 viral particles could be detected with Coomassie blue staining, and 6×10^6 viral particles could be detected with a more sensitive staining procedure using amido black.

- 6887 GENETIC RELATIONSHIP OF A PRIMATE RNA TUMOUR VIRUS GENOME TO GENES IN NORMAL MICE. (Eng.) Wong-Staal, F. (Natl. Cancer Inst., Bethesda, Md.); Gallo, R. C.; Gillespie, D. *Nature* 256(5519):670-672; 1975.

A study was conducted to determine the genetic relation between the simian sarcoma virus (SiSV) genome and genes in normal mice. SiSV was isolated from a natural sarcoma of a woolly monkey. The monkey tumor was homogenized, and a cell-free extract was placed on normal marmoset lung cells which then began to produce virus. The virus-producing cells were then inoculated into a marmoset, after which the resulting tumor was explanted and cultured. These tumor cells produced a virus (SiSV). 70S RNA was isolated from the SiSV, labeled with ¹²⁵I *in vitro*, and hybridized (60 C in 0.47 M PO₄) with DNA purified from a variety of animal tissues or cultured cell lines. SiSV RNA and cellular DNA hybrids were detected when the mixture was treated with 20 µg/ml RNase A in 0.6 M NaCl (20 min). DNA from mice or rats hybridized more with SiSV RNA (16-55% of RNA) than did DNA from other animals; appreciable hybridization was obtained from DNA of some Old World primates (9-25% of RNA) and, to a lesser extent, from New World monkeys (7-18% of RNA). DNA from chimpanzees hybridized 25% of the SiSV RNA, whereas DNA from humans hybridized only 5-10%. DNA from the lower animals studied (e.g. slug, racoon, chicken, cat, squirrel, and pig) hybridized 1-10% of the RNA. These results indicate that SiSV virus contains a genome related to the genes found in normal mice, and that a small portion of the SiSV genome is related to the genes of normal primates.

- 6888 A COMPARISON OF THE INTERNAL ANTIGENS OF SEVERAL LEUKEMIA-LYMPHOMA COMPLEX VIRUSES TRANSMITTED TO MURINE HOSTS. (Eng.) Hong, L. (Univ. Kansas, Kansas). *Diss. Abstr. Int. B* 35(4):4514; 1975.

The internal antigenic relationship of several leukemia-lymphoma complex viruses from the murine hosts was investigated with a special interest in detecting trans-species infections. Four virus strains were studied. They were AL3B, HL XI, CL1BT-C, and CL1Ba viruses, the causative agents of neoplasms that had developed in recipient mice following the inoculation of avian T-virus, human leukemic filtrate, canine leukemic cells, and canine leukemic filtrate, respectively. The viruses were propagated in mice and purified by density gradient centrifugation. Viral internal antigens were prepared from virus preparations and from neoplastic tissues. Group-

specific (gs) antigens of a "Rauscher" leukemia virus ("R"LV) that had been propagated in W/FU rats and anti-"R"LV gs serum were employed for the identification of murine leukemia virus gs-1 antigen. Feline leukemia virus (FeLV) gs antigens and anti-FeLV gs serum were employed for the detection of gs-3 antigen. Antigenic relationship of the viruses was determined by Ouchterlony technique. Based on their formation of visible precipitates with anti-"Rauscher" leukemia virus group-specific serum, the viruses were found to fall into reacting and non-reacting groups. AL3B, HL XI, and CL1BT-C viruses were in the former group, while CL1Ba virus was in the latter group. AL3B and CL1BT-C viruses possessed murine leukemia virus gs-1 antigen. They were identified as members of the murine leukemia-sarcoma viruses. Murine leukemia virus gs-1 antigen was detected in the HL XI neoplastic tissue. The HL XI virus was tentatively identified also as a member of the murine leukemia-sarcoma viruses. Neither murine leukemia virus gs-1 nor gs-3 antigen could be detected in the CL1Ba neoplasm. It was concluded that AL3B, HL XI and CL1BT-C neoplasms had developed spontaneously; they were not trans-species infections. Trans-species infection for CL1Ba neoplasm could not be ruled out by the available data.

6889 MURINE VIRUS SUSCEPTIBILITY OF CELL CULTURES OF MOUSE, RAT, HAMSTER, MONKEY, AND HUMAN ORIGIN. (Eng.) Reed, J. M. (Life Sciences Res. Div., IIT Res. Inst., 10 West 35th St., Chicago, Ill. 60616); Schiff, L. J.; Shefner, A. M.; Pooley, S. M. *Lab. Anim. Sci.* 25(4):420-424, 1975.

Studies were initiated to determine the practicality of using various tissue cultures of the Swiss mouse (pregnant and weanling), rat, Syrian golden hamster (pregnant), monkey, fertile chick egg, and tissues of human origin for the propagation of ten murine viruses isolated from laboratory animals. In addition, the cytopathogenic effects of these viruses were compared to monolayer cultures of L929, BHK-21, WI-38, BSC-1, and Vero cells. The tissue culture infectious dose was determined by the endpoint of cytopathogenic effect (CPE) and by liver pathology at necropsy. Mouse adeno virus produced CPE in L929 and BHK-21 cell cultures while mouse pneumonia virus (PVM) caused CPE in BHK-21 and Vero cell monolayers. Reo virus-type 3 produced CPE in all five cell cultures. Murine cytomegalovirus (MSGV) produced CPE only in BHK-21 cell monolayers while Sendai virus inoculation produced CPE in BSC-1 and Vero cell preparations. Nonspecific granular degeneration was observed with H-1 virus in L929, BHK-21, WI-38, and Vero cell lines and with K virus in BSC-1 cell monolayers. Swiss mouse embryo (SME) and mouse kidney (SMK) cultures supported the growth of mouse adeno, polyoma, reo-type 3, and MSGV. Reo-type 3, MSGV, and rat virus produced CPE in rat embryo (RE) cultures. Hamster kidney cultures were susceptible to reo-type 3 and MSGV. PVM and reo-type 3 produced CPE in hamster embryo cultures. Thus, seven of the ten murine viruses produced cytopathogenic effects in at least one of the cell cultures. With the exception of the rat and Sendai viruses, the viruses which exhibited CPE in test cultures had been adapted to growth in tissue culture.

Mouse hepatitis, H-1, and K viruses exhibited no evidence of viral replication. The data suggest that BHK-21 and Vero cells as well as primary SME, SMK, and RE are useful for the propagation of murine viruses isolated from laboratory rodents.

6890 PRIMATE TYPE C VIROGENES: DETECTION OF ENDOGENOUS GENE EXPRESSION IN NORMAL AND NEOPLASTIC TISSUES OF PRIMATES, INCLUDING MAN. (Eng.) Todaro, G. J. (Nat'l. Cancer Inst., Bethesda, Md.); Benveniste, R. E.; Sherr, C. J.; Calahan, R.; Lieber, M. *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 226-229.

The detection of endogenous primate type C viro-gene expression in normal and neoplastic tissues of primates is reviewed. Several new lines of evidence support the hypothesis that all somatic cells of vertebrates contain the genetic information for making a complete type C virus, and the spontaneous appearance of complete infectious type C viruses in animals and cells cultured from them has led to the hypothesis that the information for the formation of such viruses may be transmitted genetically from parent to progeny. The endogenous type C virogenes are those sets of gene sequences which code for the production of type C viruses that are an integral part of the host species' chromosomal DNA. The sets of virogenes that a particular species possesses are normally repressed, but can be activated by a variety of intrinsic and extrinsic factors. As compared with most other cellular genes, type C virogenes are unique in that they can give rise to the production of infectious type C virus particles. Endogenous type C viruses have been detected in a wide variety of mammalian species. Among the primates, type C viral genes have evolved with the species, the virogenes from more closely related genera and families showing more sequence homology than those from distantly related taxons. However, the viral genes from one group of animals can give rise to infectious particles that not only can integrate into the DNA of animals of another species, but can also be incorporated into the germ line of the latter. The genomes of exogenous infectious viruses replicating in permissive host cells evolve much more rapidly than endogenous virogenes which replicate solely as cellular genes. Normal primate and human tissues translate at least one viral structural protein. If RNA tumor viruses play a role in human cancer causation, the approaches to early diagnosis and prevention will depend on the determination of where the viral information comes from and how it is normally controlled.

6891 INDUCTION OF ENDOGENOUS MURINE C-TYPE VIRUS IN SPLEEN CELL CULTURES TREATED WITH MITOGENS AND 5-BROMO-2'-DEOXYURIDINE. (Eng.) Moroni, C. (Friedrich Miescher-Institut, Basel, Switzerland); Schumann, G.; Robert-Guroff, M.; Suter, E. R.; Martin, D. *Proc. Natl. Acad. Sci. USA* 72(2):535-538; 1975.

To develop an efficient *in vitro* method for virus induction in lymphoid cells, induction of DNA synthesis with mitogens was studied. Spleen cell cultures were prepared from 6- to 8-wk-old male BALB/c mice. Activity of reverse transcriptase (RNA-dependent DNA polymerase) preferring $A_n \cdot dT_{12-18}$ over $dA_n \cdot dT_{12-18}$ as a template-primer was used as a measure of virus release. The term virus is used although the infectivity of these particles has not been shown. A combination of 5 μ g 5-bromo-2'-deoxyuridine (BrdU) and either 16 μ g lipopolysaccharide W (LPS-W) from *Escherichia coli* or 4 μ g concanavalin A (Con A) resulted in the release of virus into the medium. Phytohemagglutinin (PHA) at 10 μ g had no effect either with or without BrdU. When the same experiment was performed with spleen cells from AKR mice known to harbor C-type viruses throughout life, elevated reverse transcriptase activity was found in LPS-stimulated cultures without added BrdU. As in BALB/c cultures, LPS had the lowest mitogenic activity as indicated by intracellular [3H]thymidine incorporation. With AKR cells, BrdU inhibited virus release. In contrast to BALB/c, no virus was induced by Con A plus BrdU. PHA or Con A alone had no effect in either strain of cells. Electron microscopy showed typical C-type virus particles. Isopycnic sucrose gradient centrifugation of supernatants from stimulated BALB/c cultures gave major peaks at 1.15 to 1.17 g/cm³, which is the density characteristic of C-type viruses. Electron microscopy of spleen cells which had released reverse transcriptase activity in parallel cultures showed typical C-type virus particles.

- 6892 DIFFERENT TYPES OF ONCOGENIC VIRUSES ASSOCIATED WITH HEMOBLASTOSIS IN MONKEYS. (Rus.) Lapin, B. A. (Inst. Experimental Pathology and Therapy of Acad. of Medical Sciences of the USSR, Sukhumi, USSR); Takovleva, L. A.; Kokosha, L. V.; Agrba, V. Z.; Chuvirov, G. N.; Kakubava, V. V. *Dokl. Akad. Nauk S.S.S.R.* 224(4):950-952; 1975.

Two oncogenic viruses; a DNA-containing herpes virus and type C oncornavirus with 65-70 S RNA and reverse transcriptase activity, were found to be simultaneously present in the serum and organs (spleen, bone marrow, lymph nodes) of Pavio hamadryas specimens with malignant lymphoma. Each of the two different viruses, present in one and the same animal, appear to be involved in carcinogenesis. The findings are analogous with observations on the participation of oncogenic DNA and RNA viruses in the genesis of Burkitt's lymphoma and lymphomatosis in chicken.

- 6893 DETECTION OF C TYPE VIRUS PARTICLES IN THE SPLEEN OF C57BL LOW-LEUKOSIS LINE MICE. (Rus.) Gogichadze, G. K. (G. M. Mukhadze Scientific-Res. Inst. Hematology and Blood Transfusion, Tbilisi, USSR). *Vopr. Virusol.* (4):486-487; 1975.

The spleen, thymus and lymph nodes of 3-4-wk-old normal C57BL low-leukosis line mice were investigated for the presence of C type virus particles by electron microscopy. Both mature particles (with

electron-microscopically dense nucleoid) and immature particles (with electron-microscopically transparent center with three concentric membranes) of type C virus were found in the spleens of 8 of 10 animals. The diameter of the particles was 100-110 nm, and that of the nucleoid was 55-60 nm. In most cases, the virus particles were localized in the extracellular space, and, in a few cases, in the cytoplasmic vacuoles. The virus particles were usually isolated or were present in pairs. An aggregate of virus particles in the intracellular space was found in one case only. Aggregates of virus particles on the plasma membrane were found in certain cases. In most cases, the virus particles were localized in megakaryocytes. The latent virus was found to be identical morphologically with that inducing leukemia in mice and birds. The presence of this latent oncornavirus indicates the mediator role of this virus under the effect of physical and chemical factors on microorganisms. The high susceptibility of C57BL line mice to radiation and chemical carcinogenesis is apparently due to the synergism of these factors with the oncornavirus. No type C virus particles were found in the thymus and lymph nodes.

- 6894 ISOLATION OF A TYPE C VIRUS (FS-1) FROM THE EUROPEAN WILDCAT (*FELIS SYLVESTRIS*). (Eng.) Lieber, M. M. (National Cancer Inst., Bethesda, Md. 20014); Benveniste, R. E.; Sherr, C. J.; Todaro, G. J. *Virology* 66(1):117-127; 1975.

The DNA of the European wildcat (*Felis sylvestris*) contains sequences that hybridize to [3H]DNA transcripts of the RNA of domestic cat type C viruses of the RD-114/CCC group. To determine if the sequences could code for the production of infectious virions, tissues from a European wildcat were cocultivated with established cell lines from heterologous species known to be permissive for the replication of endogenous domestic cat type C viruses. Both a syncytium-forming ("foamy") and a type C virus were isolated, and the type C viral component was resolved by passaging the mixed virus stock in cells that are relatively resistant to infection by feline syncytium-forming viruses. The European wildcat type C virus (FS-1) was found to be highly related to viruses of the RD-114/CCC group by viral host range and interference criteria. FS-1 contained a reverse transcriptase and major group-specific protein (p30) with antigenic determinants similar to those of the homologous proteins of RD-114 and [3H]DNA transcripts of FS-1 RNA hybridized extensively to the RNA of endogenous domestic cat type C viruses. Like viruses of the RD-114/CCC group, FS-1 was found related by several criteria to endogenous baboon type C viruses. The results indicate that European wildcats contain endogenous type C virogenes that can code for the production of infectious type C particles.

- 6895 A POSSIBLE ASSOCIATION OF ONCORNAVIRUS OF TYPE D WITH SOME CANCER TYPES. (Rus.) Zhdanov, V. M. (The D. I. Ivanovsky Inst. of Virology of the USSR Acad. of Medical Sciences, Moscow, USSR); Trushinskaya, G. N.; Zorin, E. V.; Bukrins-

kaya, A. G.; Mazurenko, N. N.; Il'in, K. V.; Zairov, G. K.; Demidova, S. A.; Perekrest, V. V.; Tolmacheva, V. D. *Vopr. Onkol.* 21(6):77-83; 1975.

The possible association of HEp2 cell oncornavirus type D (antigenically similar to Mason-Pfizer virus) with normal and neoplastic human cells was studied by molecular hybridization of nucleic acids of HEp2 cell oncornavirus type D with cell nucleic acids. Normal human cells were found to contain no sequences homologous to the virus concerned, which indicates that the cytoplasm of normal human cells contains no RNAs homologous to the DNA transcripts of this virus, which means that this virus is not endogenous for the human organism. Similar findings were obtained also for tissues from patients with lymphogranulomatosis, indicating that the genesis of lymphogranulomatosis is not connected with the participation of this virus. The molecular hybridization tests revealed the presence of virus-homologous sequences in 2 of 8 of breast cancer patients, in 2 of 2 patients with skin cancer, in ovarian tumors, but not in gastric cancer, uterine fibrosarcoma, or cancer of the parotid gland. The hybridization tests were positive mainly for hormone-associated tumors, which indicates that oncornavirus type D or another similar virus participates in the genesis of or is at least associated with these forms of cancer.

- 6896 IDENTIFICATION OF HEAT-DISSOCIABLE RNA COMPLEXES IN TWO PORCINE CORONAVIRUSES. (Eng.) Garwes, D. J. (Agricultural Res. Council, Compton, Newbury, Berkshire RG16 0NN, U.K.); Pocock, D. H.; Wijaszka, T. M. *Nature* 257(5527):508-510; 1975.

Polyacrylamide gel electrophoresis of RNA extracted from purified preparations of transmissible gastroenteritis virus (TGEV) isolated from pig kidney cells, and of RNA from a second porcine coronavirus, hemagglutinating encephalomyelitis virus (HEV), revealed an RNA component that dissociates in a way closely resembling dissociation of the genome of oncogenic RNA viruses. The mobilities of RNA extracted from TGEV and HEV at 20 and 100 C were compared with those of Rous sarcoma virus (RSV) held at the same temperatures. By this method, the RNA complexes extracted from the two coronaviruses were indistinguishable in size from the 60-70S component of RSV RNA; similarly, after heating, the TGEV and HEV RNA components were comparable in size to the RSV 35S RNA. However, there seemed to be more heterogeneity in the coronaviral 35S RNA band than in the RSV equivalent. When TGEV was held at 4 C for 20 days before extraction at 20 and 100 C, the 60-70S complex appeared to be intact; on melting, however, the complex liberated only small fragments of RNA of approximately 4S. This suggests that the virus preparations have an associated ribonuclease capable of producing breaks in the 35S strand while they are complexed in the 60-70S form. Whether the large amount of 4S RNA detected in all HEV preparations examined represents degraded viral RNA or host transfer RNA associated with the virions is unknown. The similarity in the structure of the genomes of

coronaviruses and oncornaviruses has interesting implications for the phylogeny of the RNA tumor viruses.

- 6897 QUALITATIVE COMPLEMENTATION TEST FOR TEMPERATURE-SENSITIVE MUTANTS OF HERPES SIMPLEX VIRUS. (Eng.) Chu, C.-T. (Baylor Coll. Medicine, Houston, Tex. 77025); Schaffer*, P. A. *J. Virol.* 16(5):1131-1136; 1975.
- 6898 COMPARISON OF THE VIRION PROTEINS SPECIFIED BY HERPES SIMPLEX VIRUS TYPES 1 AND 2. (Eng.) Cassai, E. N. (Dept. Microbiology, Univ. Chicago, Chicago, Ill. 60637); Sarmiento, M.; Spear*, P. G. *J. Virol.* 16(5):1327-1331; 1975.
- 6899 ULTRAMORPHOMETRY OF THE CELL CULTURE OF HAMSTER EMBRYONIC FIBROBLASTS IN TRANSFORMATION WITH ROUS SARCOMA VIRUS. (Rus.) Iagubov, A. S. (P. A. Herzen Res. Inst. Oncology, Moscow, USSR); Ageenko, A. I.; Chutkov, N. A. *Vopr. Onkol.* 21(7):62-66; 1975.
- 6900 INHIBITION OF ROUS SARCOMA VIRUS REPRODUCTION BY A RIFAMYCIN DERIVATIVE. (Eng.) Szabo, C. (Univ. California, Berkeley); Bissell, M. J.; Calvin, M. *Fed. Proc.* 34(3):531; 1975.
- 6901 PLASMA MEMBRANE VESICLES FROM SV-3T3 CELLS TRANSPORT THE RIBOSE MOIETY OF INOSINE BY A GROUP TRANSLOCATION MECHANISM. (Eng.) Quinlan, D. C. (Worcester Found. Exp. Biol., Shrewsbury, Mass.); Hochstadt, J. *Fed. Proc.* 34(3):556; 1975.
- 6902 EARLY CYTOPLASMIC VACUOLIZATION OF AFRICAN GREEN MONKEY KIDNEY CELLS BY SV 40. (Eng.) Miyamura, T. (Dept. Enteroviruses, Natl. Inst. Health, Nakato, Musashimurayama, Tokyo 190-12, Japan); Kitahara, T. *Arch. Virol.* 48(2):147-156; 1975.
- 6903 POLYOMA VIRUS GENE FUNCTIONS IN CELL TRANSFORMATION. (Eng.) Major, E. O. (Univ. Illinois Medical Center, Chicago, Ill.); D'Agostino, R.; di Mayorca, G.; Noonan, K. D. *Proc. Int. Cancer Congr. 11th. Vol. 2 (Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975. pp. 207-213.
- 6904 STUDY OF BIOLOGICAL, MORPHOLOGICAL AND IMMUNOLOGICAL FEATURES OF CELLS TRANSFORMED *IN VITRO* BY BOVINE ADENOVIRUS TYPE 3. (Rus.) Strizhachenko, N. M. (K. I. Skryabin Acad. Veterinary Science, Moscow, USSR); Graevskaia, N. A.; Karmysheva, V. Ia.; Levenbuk, I. S.; Abramova, V. P.; Siurin, V. N. *Vopr. Virusol.* (3):293-297; 1975.

- 6905 GENETIC SUSCEPTIBILITY OF CHICKEN X QUAIL HYBRID EMBRYOS TO AVIAN RNA TUMOUR VIRUSES. (Eng.) Pani, P. K. (Houghton Poultry Res. Station, Houghton, Huntingdon Cambs., PE172 DA, England). *J. Gen. Virol.* 28(1):159-163; 1975.
- 6906 THE SIZE DISTRIBUTION OF NUCLEAR AND CYTOPLASMIC VIRUS-SPECIFIC RNA MOLECULES IN RAT EMBRYO CELLS TRANSFORMED BY ADENOVIRUS TYPE 2. (Eng.) Sekikawa, K. (Sapporo Medical Coll., Sapporo, Japan); Shimada, K.; Fujinaga, K.; Ito, Y. *Tumor Res.* 9(1):42-48; 1974.
- 6907 DEMONSTRATION OF PAPOVAVIRUS TUMOR ANTIGEN IN BRAIN TUMORS [abstract]. (Eng.) Becker, L. E. (Johns Hopkins Univ. Sch. Medicine, Baltimore, Md.); Narayan, O.; Johnson, R. T. *J. Neuropathol. Exp. Neurol.* 34(1):95; 1975.
- 6908 STUDY ON TRANSPLANTABLE, MELANIN CONTAINING HAMSTER PAPOVA VIRUS-INDUCED SKIN TUMOURS IN SYRIAN HAMSTER. (Ger.) Bender, E. (Zentralinstitut für Krebsforschung Akademie Wissenschaften DDR, Bereich Experimentelle Krebsforschung, DDR-115 Berlin-Buch, Lindenberger Weg 70, East Germany); Graffi, A.; Niezabitowski, A.; Wildner, G. P.; Schneiders, F. *Arch. Geschwulstforsch.* 45(3):244-254; 1975.
- 6909 THE DAMAGING EFFECT OF TWO SIMIAN VIRUSES ON MAMMALIAN CELL CHROMOSOMES. (Rus.) Mus-tafina, A. N. (Inst. Poliomyelitis and Viral Encephalitis, Moscow, U.S.S.R.); Sabin, M. A.; Grachev, V. P. *Vopr. Virusol.* (3):327-330; 1975.
- 6910 EFFECT OF VIRAL INFECTION ON PHOSPHATIDYL CHOLINE BIOSYNTHESIS. (Eng.) Hoffman, D. R. (Univ. North Dakota Med. Sch., Grand Forks); Skurdal, D. N.; Cornatzer, W. E. *Fed. Proc.* 34(3):933; 1975.
- 6911 RESTRICTION OF FELINE LEUKEMIA VIRUS AND BALB/c ENDOGENOUS VIRUS PRODUCTION IN CAT-MOUSE HYBRID CELLS [abstract]. (Eng.) O'Brien, S. J. (Nat'l. Cancer Inst., Bethesda, Md. 20014); Simonson, J. M.; Boone, C. W. *Genetics* 80(3/Part 1/ Suppl.):s61-s62; 1975.
- 6912 CERTAIN BIOCHEMICAL PROPERTIES OF BOVINE LEUKEMIA VIRUS (BLV) [abstract]. (Fre.) Kettmann, R. (Laboratoire de Chimie Biologique, Université Libre de Bruxelles, Belgium); Mammerickx, M.; Dekegel, D.; Ghysdael, J.; Portelelle, D.; Burny, A. *Arch. Int. Physiol. Biochim.* 83(1):193-194; 1975.
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- 6914 INHIBITION AND ENHANCEMENT OF FRIEND LEUKEMIA VIRUS BY PYRAN COPOLYMER. (Eng.) Schuller, G. B. (Medical Coll. of Virginia, Virginia Commonwealth Univ., Richmond, Va. 23298). *Cancer Res.* 35(8):1915-1920; 1975.
- 6915 ABORTIVE MYXOVIRUS INFECTION IN EHRLICH ASCITES CARCINOMA CELLS. ANALYSIS OF VIRUS-SPECIFIC STRUCTURES IN THE ASCITIC FLUID. (Rus.) Asadullaev, T. A. (G. M. Musabekov Scientific-Res. Inst. Virology, Microbiology and Hygiene, Moscow, U.S.S.R.); Gitelman, A. K.; Burkinskaia, A. G. *Vopr. Virusol.* (3):278-282; 1975.
- 6916 HUMAN AND PRIMATE POXVIRUSES: I. GROWTH CHARACTERISTICS OF CYTOLYTIC AND TUMOR VARIANTS. (Eng.) Sheek, M. R. (Univ. Kansas Medical Center, Rainbow Boulevard at 39th Street, Kansas City, Kans. 66103); Chapman, A. L.; Wenner, H. A. *Arch. Virol.* 48(1):47-61; 1975.
- 6917 INCIDENCE OF CMV ISOLATION AND RELATED PATHOLOGY IN AUTOPSY TISSUE [abstract]. (Eng.) Macasaet, F. F. (Mayo Clinic, Rochester, Minn. 55901); Holley, K. E.; Smith, T. F.; Keys, T. F. *Am. J. Clin. Pathol.* 63(4):596-597; 1975.
- 6918 STRESS EFFECTS OF THE LDH-VIRUS IN ALTERING THE GARDNER TUMOR IN MICE [abstract]. (Eng.) Spackman, D. (Pac. Northwest Res. Found., Seattle, Wash.); Riley, V. *Proc. Am. Assoc. Cancer Res.* 16:170; 1975.
- 6919 EVIDENCE FOR A VIRAL MATURATION COMPLEX IN PARVOVIRUS INFECTED CELLS [abstract]. Gautschi, M. (Inst. für Hygiene und Medizinische Mikrobiologie, CH-3000 Bern, Switzerland); Siegl, G. *Experientia* 31(6):738; 1975.
- 6920 CHARACTERIZATION OF PURIFIED DNA-RELAXING ENZYME FROM HUMAN TISSUE CULTURE CELLS. (Eng.) Keller, W. (Cold Spring Harbor Lab., Cold Spring Harbor, N.Y. 11724). *Proc. Natl. Acad. Sci. USA* 72(7):2550-2554; 1975.
- 6921 THE ROLE OF DIVALENT ION COMPLEX FORMATION IN PYRAN INHIBITION OF NUCLEIC ACID BIOSYNTHESIS [abstract]. (Eng.) Fiel, R. J. (Roswell Park Memorial Inst., Springville Lab., Springville, N.Y. 14141); Musser, D. A.; Munson, B. R. *Proc. Am. Assoc. Cancer Res.* 16:49; 1975.
- 6922 ON THE USE OF CHLORAMINE-T TO IODINATE SPECIFICALLY THE SURFACE PROTEINS OF INTACT ENVELOPED VIRUSES. (Eng.) Montelaro, R. C. (Biophysics Lab., Graduate Sch., Univ. Wisconsin, Madison, Wis. 53706); Rueckert, R. R. *J. Gen. Virol.* 29/Part 1:127-131; 1975.

See also:

- * (Rev): 6615, 6616, 6617, 6618, 6619, 6620, 6621, 6622, 6623, 6624, 6633, 6656, 6657, 6658, 6663, 6669
- * (Chem): 6709
- * (Immun): 6928, 6946, 6948, 6949, 6950, 6951, 6952, 6953, 6954, 6955, 6956, 6969, 6978, 6984, 6985, 6990, 7005
- * (Path): 7050, 7081
- * (Epid-Biom): 7144

- 6923 BINDING OF α -FOETOPROTEIN TO MURINE T CELLS. (Eng.) Dattwyler, R. J. (Mayo Med. Sch., Rochester, Minn.); Murgita, R. A.; Tomasi, T. B., Jr. *Nature* 256(5519):656-657; 1975.

The cell types involved in the immune reaction that are affected by α -fetoprotein (AFP) were detected by direct immunofluorescence in T cells, B cells and macrophages of C57BL female mice (6 to 10-wk-old). AFP was isolated from Ha/ICR mice amniotic fluid during the late second trimester of pregnancy. AFP binding cells were found in the spleen (18% of the cells bound to AFP, lymph nodes (23%) and cortisone-resistant thymocytes (6%), but not in the bone marrow (2%) or nude mouse spleen cells (<1%). When adult mouse spleen cells were treated with anti-Fab or anti- θ plus complement to produce lymphoid preparations depleted of B and T cells, respectively, AFP was found to bind to cells that were not adherent to nylon wool and that were destroyed by anti- θ plus complement (34%). There was only a small amount of AFP binding to macrophages (4%) obtained from peritoneal exudate cells injected with thioglycolate. No binding was observed with B cell-enriched populations or in the spleens of nude mice. Thus, the T cell was the major cell type affected by AFP. Only a fraction (1/3) of T cells bound to AFP suggesting that a subclass of T cells was involved in AFP suppression. In addition, the relatively fewer numbers of thymocytes and cortisone-resistant thymus cells (as compared to peripheral spleen T cells) that bind to AFP suggest that AFP binding involves the detection of surface receptors that require additional maturation after peripheralization from the thymus.

- 6924 α -FETOPROTEIN SYNTHESIS IN CULTURED CELLS: STUDIES ON YOSHIDA SARCOMA AND ASCITES HEPATOMA *IN VITRO*. (Eng.) Isaka, H. (Sch. Medicine, Kagoshima Univ., Kagoshima, Japan). *Ann. NY Acad. Sci.* 259:74-79; 1975.

The effects of cyclic AMP (cAMP) and/or dibutyryl cAMP, Na-butylate, 5'-AMP, theophylline, and other chemical substances on α -fetoprotein (AFP) synthesis in Yoshida sarcoma and ascites hepatoma AH-66 cultures were examined. The substances tested were dissolved in the culture medium at the start of cultivation. Cell proliferation was measured by hemocytometry and AFP concentrations by ^{125}I -radioimmunoassay, double-antibody method of the cell-free three- or four-day culture medium. Addition of cAMP (1, 2, or 5 mM) to Yoshida sarcoma and ascites hepatoma AH-66 culture media resulted in inhibition of cell proliferation. Theophylline (0.1 mM) plus cAMP (0.5 mM) induced greater inhibition of cell growth than the same concentrations of either substance alone in the Yoshida sarcoma cells. Theophylline or cAMP added to the medium of both cultures resulted in increased AFP production. In AH-66 cultures, addition of dibutyryl cAMP caused a greater increase in AFP production than c-AMP treated cells. With higher concentrations of either Na-butylate or 5'-AMP, AH-66 cells produced greater amounts of AFP. Addition of chaetoglobosin, 5-bromodeoxyuridine, dexamethasone, insulin, glucagon, bleomycin, and N-n-butyl nitrosourea caused no

increase in AFP production in the AH-66 medium; however, chaetoglobosin addition resulted in the formation of multiple nuclei. The authors suggest that the differential increase in AFP production observed with the addition of cAMP, dibutyryl, Na-butylate, 5'-AMP may be due to differing abilities of these substances to penetrate the cells.

- 6925 BIOCHEMICAL AND IMMUNOLOGICAL STUDIES OF SOME CARCINOFETAL ENZYMES. (Eng.) Hatzfeld, A. (Institut de Pathologie Moléculaire, Paris, France); Weber, A.; Schapira, F. *Ann. NY Acad. Sci.* 259:287-297; 1975.

Immunodiffusion and extensive purification of rat carcinofetal enzymes, aldolase C and pyruvate kinase (PK), were carried out; and the relation of these enzymes to fetal isozymes of normal tissue was investigated. Carcinofetal aldolase C was derived from a Zajdela ascitic hepatoma while carcinofetal PK was purified from a poorly differentiated hepatoma, Reuber H 178. With antiserum anti-aldolase A and C, a reaction of complete identity occurred between brain, fetal liver, and hepatoma; no line was seen with adult liver. The aldolase activity ratio of aldolase C substrates, fructose-1,6-diphosphate (FDP) to fructose-1-phosphate (F1P), was 7.3 for the brain tissue and 7.4 for the hepatoma. The Michaelis constants for FDP and F1P were 0.2 mM and 17 mM, respectively, for the brain tissue and 0.3 mM and 18 mM, respectively, for the hepatoma. In both tissues, the molecular weight of aldolase C was 37,000, and arginine was found to be the N-terminal amino acid. The amino acid composition of both the brain and the hepatoma aldolase C was similar. The PK of poorly differentiated hepatoma resembled the placental PK by its electrophoretic migration at pH 7.0 on starch gel. Both the cancerous and the placental PK were activated by fructose diphosphate in the presence of a nonsaturating concentration of substrate phosphoenolpyruvate. There was a reactivity of total identity between the precipitation lines of placental and hepatoma PK when tested against antiserum anti-PK II (a type of PK found in the liver). The results indicate that the aldolase C and the PK of hepatoma are the same as those found in normal tissue. In addition, the resurgence of fetal antigens was discussed in relation to that of fetal isozymes. The authors suggest that a rough correlation exists between the growth rate of tumors and the extent of resurgence of fetal isozymes with the disappearance of the adult ones. No correlation was found between the level of fetal antigens and the growth rate of tumors.

- 6926 IMPORTANCE OF THE CARCINOEMBRYONIC ANTIGEN (CEA) IN CLINICAL MEDICINE AND IN BASIC CANCER RESEARCH. (Eng.) Mach, J. P. (Ludwig Inst. Cancer Res., 21 rue du Bugnon, 1011 Lausanne, Switzerland); Jaeger, P.; Pettavel, J.; Merenda, C.; Carrel, S. *Proc. Int. Cancer Congr. 11th.* Vol. 1 (*Cell Biology and Tumor Immunology*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 249-253.

The use of carcinoembryonic antigen (CEA) as a biological marker of some carcinomas in selected clinical situations was demonstrated. In addition, the biological properties of CEA (e.g., biosynthesis, release in circulation, immunogenicity, and the accessibility of CEA to heterologous specific antibodies injected i.v.) were studied in nude mice bearing heterografts of human colon carcinoma. CEA was measured by radioimmunoassay before treatment in 101 patients with colon or rectum carcinoma and in 110 normal individuals. The majority of the carcinoma patients (72) had CEA levels over 5 ng/ml as compared to only eight of the controls (7 smokers and one nonsmoker). In 45 patients undergoing complete tumor resection, the CEA level dropped to normal values in all but five cases; these patients subsequently showed a rise in CEA and tumor relapse. In 19 patients with distant metastases or incomplete tumor resection, the CEA levels remained stable after surgery or showed only a moderate fall. In eight patients later found to have a tumor relapse, the elevation in CEA level preceded the clinical diagnosis of tumor relapse by several months. These results show that in diagnosed cases of colon carcinoma, repeated CEA measurements can help detect recurrence of colon carcinoma long before any clinical symptoms or any change in conventional laboratory tests are evident. In the second experiment, direct immunofluorescence revealed that CEA produced by the grafted carcinoma had the same histological localization as in the primary tumor. Circulating CEA was detected by double antibody radioimmunoassay in 20 nude mice with a graft larger than 0.5 g; the highest circulating levels were observed in animals with well differentiated tumors. None of the tumor bearing nude mice were found to have anti-CEA antibodies by a direct binding assay; however, BALB/c mice produced anti-CEA antibodies when immunized with purified CEA, suggesting that CEA is a thymus-dependent antigen. The results suggest that labeled anti-CEA antibodies could be used as radioactive tracers for the localization of human tumors.

6927* ELECTRON MICROSCOPY AND PHYSICAL CHARACTERIZATION OF THE CARCINOEMBRYONIC ANTIGEN.

(Eng.) Slayter, H. S. (Sidney Farber Cancer Center, Boston, Mass. 02115); Coligan, J. E. *Biochemistry* 14(11):2323-2330; 1975.

Carcinoembryonic antigen (CEA), a glycoprotein material purified from human tumors (liver metastases of primary adenocarcinomas of the colon), was visualized by electron microscopy. At neutral pH, it consisted largely of relatively homogeneous, morphologically distinctive twisted rod or cruller shaped particles, 9 x 40 nm. The particle length was considerably diminished at pH 4.0, which correlated with a known diminution of charge. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis indicated a molecular wt of 180,000 in the peak region of the CEA band for both 10 and 15% acrylamide. When native CEA was treated with neuraminidase, reduced, and alkylated, a relatively compact random coil was produced, whereas reduction and alkylation without neuraminidase treatment produced a less compact random configuration, as determined by sedimentation studies and by electron microscopy. Electrophoretic

migration was apparently unaffected by reduction and alkylation. Thus the characteristic CEA particle appears by several lines of evidence to be substantially folded into a recognizable tertiary structural arrangement. These and other data suggest a model for CEA: a core folded to 40 nm, from which numerous carbohydrate side chains protrude.

6928 EMBRYONIC ANTIGENS SHARED BETWEEN CHEMICALLY INDUCED LYMPHOSARCOMAS AND FIBROSARCOMAS OF THE MOUSE. (Eng.) Menard, S. (Div. Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, 20133 Milan, Italy); Colhaghi, M. I. *J. Natl. Cancer Inst.* 54(2):479-481; 1975.

An antiserum was obtained by the immunization of C57BL/HeDp mice with a pool of 7,12-dimethylbenz[a]anthracene (DMBA)-induced fibrosarcomas from C3Hf/Dp mice. This antiserum exerted a specific cytotoxic activity *in vitro* on chemically induced (urethane or N-nitrosomethylurea) lymphosarcomas in C57BL/HeDp mice. Conversely, C57BL/HeDp spleen cells sensitized against chemically induced lymphosarcomas or embryo cells (C3Hf/Dp) were cytotoxic for plated cells of syngeneic DMBA-induced fibrosarcomas. Absorption studies with antiembryo and antilymphoma antisera showed that embryonic antigens were shared between lymphosarcomas and fibrosarcomas and that all serologically defined antigens present on lymphoma cells, including virus-related antigens, were also on fibrosarcoma cells.

6929 TUMOR-ASSOCIATED ANTIGENS IN ISOANTIGENIC VARIANTS OF A 3-METHYLCHOLANTHRENE-INDUCED SARCOMA. (Eng.) Oth, D. (Unit 95 of INSERM, Plateau de Brabois, 54500 Vandoeuvre-Les-Nancy, France); Berebbi, M.; Meyer, G. *J. Natl. Cancer Inst.* 55(4):903-908; 1975.

A sarcoma was induced in an (A.CA x A.BY)_{F1} mouse with 3-methylcholanthrene. Two isoantigenic variants were selected by loss of one H-2 antigen. The tumor-associated transplantation antigens (TATA) of these variants were compared as to their specificities in (A.CA x A.BY)_{F1} mice. Both transplantation and indirect membrane immunofluorescence tests revealed that TATA of both variants did not cross-react. Thus selecting against different H-2 antigens also selected different TATA. Karyotype studies suggested that both variants originated from a unique clone. The data support the view that TATA and H-2 antigens are not independent. The problem of defining the nature of their possible interdependence is of growing importance since noncrossing TATA are found not only in chemically induced tumors but also in physically induced and virus-induced neoplasms.

6930 THE HL-A7 HISTOCOMPATIBILITY ANTIGEN IN SARCOIDOSIS IN RELATION TO TUBERCULIN SENSITIVITY. (Eng.) Persson, I. (Norre Hosp., Copenhagen, Denmark); Ryder, L. P.; Nielsen, L. S.; Svejgaard, A. *Tissue Antigens* 6(1):50-53; 1975.

Eighty cases of sarcoidosis were investigated for the presence or absence of the HL-A7 histocompatibility antigen. In all except eight patients a histological verification of the diagnosis was obtained by mediastinoscopy or liver biopsy. The HL-A7 antigen was not increased in the entire group. However, in the group of 23 patients with a negative sensitivity to tuberculin after the appearance of the disease there was a significant increase compared with controls. In the patients with a positive reaction, there was a complete absence of HL-A7. The HL-A system therefore does not seem to influence the liability to contract sarcoidosis, but once this condition has developed, HL-A7 positives are more likely to lose cellular immunity to tuberculin and to reveal symptoms.

- 6931 IMMUNOLOGICAL PROFILE OF CANCER HIGH RISK GROUP--IMMUNE REACTION TO HB ANTIGEN IN PRIMARY HEPATOCELLULAR CARCINOMA IN ASIA AND AFRICA. (Eng.) Nishioka, K. (Natl. Cancer Center Res. Inst., Tokyo, Japan). *Proc. Int. Cancer Congr. 11th. Vol. 4 (Cancer Campaigns, Detection, Rehabilitation, Clinical Classifications)*. Florence, Italy, October, 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 177-182.

The relation between the hepatitis virus and primary hepatocellular carcinoma (HCC) was investigated by the comparison of immunologic profiles in HCC endemic areas, Asia and Africa. HB antigen and antibody were detected by immune adherence hemagglutination and passive hemagglutination, respectively. Among 15,953 Asian and African normal donors sampled, HB antigen was detected in 3.7% and HB antibody in 20.3% of the sera examined, ten-times higher than in the Western European or North American populations. HB antigen was positive in 40.6%, 28.8%, 34.1% and 48.3% in patients with acute hepatitis, chronic hepatitis, liver cirrhosis, and HCC, respectively. An extremely high risk was demonstrated for the HB antigen positive group for hepatitis, liver cirrhosis, and HCC. The HB antibody positive rate was 18.4%, 18.3%, 14.5%, and 6.7% in acute hepatitis, chronic hepatitis, liver cirrhosis, and HCC, respectively. The antibody positive rate of hepatitis and cirrhotic patients did not differ from the rate of normal population, other cancer patients, and hospitalized patients. Subtype studies revealed that aYW was predominant in west Africa to India; adw in Kenya, Indonesia, and the Philippines; and adr in Japan, China, Burma, Thailand, and Malaysia. In all of these areas, except Australia, the presence and frequency of HBAG subtypes in liver disease patients corresponded with the pattern in the normal population. The authors conclude that the immunological profile observed in HCC in Asia and Africa is characterized by: 1) a higher prevalence of HBV infection in endemic areas; 2) association with a sequence of liver disease; 3) extremely high risks to these specific liver diseases in the HBAG positive group; 4) significantly low risk to HCC in HB antibody positive group; 5) higher (80 to 100%) antigenemias rate of HBAG without antibody response in the HCC grouping, suggesting the possibility of immunologi-

cal tolerance to HBV infection in HCC; and 6) the maintenance of the HB antigen subtype in each ethnic group in HCC areas in hepatitis, liver cirrhosis and HCC patients. In addition, the authors discuss observations which support their theory that maternal transmission from HB antigen positive mothers to newborn babies at delivery is the most essential route of infection.

- 6932 IMMUNOLOGICAL DEVIATIONS ACCOMPANYING THYMOMAS AND THEIR MECHANISMS. (Pol.) Mackiewicz, S. (Zaklad Immunologii AM, Szkolna 8/12, 60-967 Poznan, Poland). *Nowotwory* 25(1):57-62; 1975.

The function of the thymus and its role in the development of the peripheral lymphoid system, the differentiation of T and B lymphocytes and immunological surveillance are discussed. Hyperplasia of the thymic medulla or thymomas is accompanied by a variety of clinical syndromes. These include myasthenia gravis, acquired hypogammaglobulinemia, aplastic anemia, diseases of the connective tissue (scleroderma, rheumatoid arthritis, lupus, Sjogren's syndrome, myositis) acquired hemolytic anemia, mono- and polyclonal gammopathies, Cushing's syndrome, cytomegalovirus infections, candidiasis and neoplasms of different organs (not specified). The question of whether there is a common cause for the occurrence of these syndromes and the development of thymoma remains unresolved. During pathologic states of the thymus the function of inductors which regulate the maturation of lymphocytes is disturbed and there is an excessive liberation of inhibitors. Using different thymus derived humoral substances it is possible to unmask a variety of receptors on the surface of lymphocytes (theta 1, theta 2, TL, LY, LY2, LY3 and G9) indicating the complexity of origin of immunocompetent lymphocytes.

- 6933 INHIBITION OF MITOSIS AND TRITIATED DNA PRECURSOR UPTAKE IN HUMAN LEUCOCYTE CULTURES BY RAT LYMPH NODE EXTRACT. (Eng.) Mills, J. (Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, Great Britain); Bishun, N. P.; Williams, D. C. *Cytobios* 12(46):89-93; 1975.

The mitotic response and tritiated DNA precursor uptake of human peripheral lymphocytes to lymph node extract from rats of different age groups was investigated. Blood for peripheral leukocyte cultures was obtained from healthy donors and lymph nodes were taken from male Sprague-Dawley rats of three age groups (2 to 3 wk, 2 to 3 months, and 6 to 9 months). Lymph node extract was added to the blood culture and controls as follows: 1) 1 mg of extract at 72, 48, and 24 hr of culture; 2) 2 mg at 72, 48, 24, and 0 hr; 3) for 72 hr, 1 mg, 2 mg, and 3 mg of extract were added to the cultures; and 4) for the last 48 hr of culture, 1 mg, 2 mg, and 3 mg of extract were added. Mitotic indices were calculated as the number of metaphase spread/1,000 cells. The effect was dose-related as tritiated thymidine uptake decreased with increasing concentrations. No difference of effect was observed among the younger groups; however, a small difference was noticed between the oldest group and

the other two groups at the two highest concentrations. Inhibition was least when the extract was present for only 24 hr, the stimulatory mechanism already having taken place and the cells continued to synthesize DNA. This investigation substantiated previous studies stating that a depressed DNA synthesis was observed with increasing concentrations of extract with respect to time. The authors conclude that the lymph node extract is not toxic, but depresses DNA synthesis and is dose-related.

6934 A RAPID PHYTOHEMAGGLUTININ INDUCED ALTERATION IN LYMPHOCYTE POTASSIUM PERMEABILITY.

(Eng.) Segel, G. B. (Univ. Rochester Sch. Medicine, Rochester, N.Y.); Hollander, M. M.; Gordon, B. R.; Klemperer, M. R.; Lichtman, M. A. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):327-335; 1975.

In order to examine the effect of phytohemagglutinin (PHA) on lymphocyte K^+ and Na^+ metabolism, the cation content of male Sprague-Dawley rat and normal human lymphocytes were determined after treatment with mitogenic concentrations of PHA. The exposure of rat and human lymphoid cells to 30 μ g PHA resulted in an apparent decrease in cellular K^+ without a significant change in cellular Na^+ when the cells were washed with isotonic Hepes buffered choline chloride prior to cation determination. The apparent reduction in total cellular Na^+ plus K^+ concentration, however, was not accompanied by a change in cell volume. It was postulated that the constant cell volume could occur only if the lost intracellular K^+ was exchanged for an external cation during the washing procedure used to prepare cells for Na^+ and K^+ measurement. The inference was supported by the quantitative recovery of lost cellular K^+ in the choline chloride washing solution and the demonstration that a comparable proportion of $^{86}Rb^+$ (K^+ analogue) $^{42}K^+$ was lost from prelabelled cells during choline chloride washing. Use of medium 199 with Hanks salts, 150 mM NaCl, or 100 mM $MgCl_2$ as the washing solution did not prevent K^+ exchange although exchange was less in the presence of $MgCl_2$. These findings indicate that PHA produces a rapid alteration in lymphocyte plasma membranes so as to allow abnormal K^+ exchange. This observation is of importance because investigators who measure intracellular solutes in PHA-treated lymphocytes must consider the possibility of loss during preparative washes. Also, changes in membrane permeability following PHA-treatment may modulate mitogenesis and/or permit the transmission of chemical messages between cells.

6935 CHANGES OF ENZYME ACTIVITIES IN SPLEEN LYMPHOCYTES FROM TUMOR-BEARING RATS.

(Eng.) Saijo, N. (Nat'l. Center Hosp., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan); Niitani, H.; Taniguchi, T.; Kawase, I.; Kimura, K. *Gann* 66(3):253-257; 1975.

The induction of concomitant immunity was studied in male Donryu rats with Yoshida ascities sarcoma cells. The changes of enzyme activity in spleen lymphocytes were also examined in normal and tumor-bearing rats. Thirty rats were inoculated sc with 5×10^6 viable

Yoshida ascities sarcoma cells. Seven days later, ten of these rats were similarly inoculated, and ten were inoculated with the same number of Sato lung carcinoma cells. Two weeks after the initial inoculation, the animals were sacrificed and the tumor weight was determined. Spleen lymphocytes were pooled from 10-15 sarcoma-treated and normal rats. The activities of ATPase, acid phosphatase, and alkaline phosphatase in intact cells, whole-cell homogenate, and in microsomal and mitochondrial fractions were then determined. Concomitant immunity was detected one week after transplantation of tumor cells. Extended metastases were found two weeks after transplantation. The enzyme activities of ATPase and acid phosphatase were definitely higher than that of normal rat one week after transplantation, but decreased to a level lower than normal two weeks later. On the other hand, alkaline phosphatase activity increased three times at one week after the transplantation and remained at the same level two weeks later. It is concluded that changes in the reactivity of host lymphocytes against the tumor are reflected in ATPase activity.

6936 THE EFFECT OF T LYMPHOCYTE DEFICIENCY ON TUMOR INDUCTION AND GROWTH. (Eng.) Gillette, R. W. (Melo Laboratories, Inc., Springfield, Va. 22151); Fox, A. *Cell Immunol.* 19(2):328-335; 1975.

The effect of T lymphocyte deficiency, which occurs in thymectomized, X-irradiated, bone marrow-reconstituted mice (TXB) or in nude mice, was studied in relation to the effect on tumor induction and growth. BALB/c mice were thymectomized and then given 800 R whole body irradiation two weeks later. They were reconstituted within six hours by injection of 5×10^7 viable syngeneic bone marrow cells. The animals were injected sc with 0.2 mg methylcholanthrene two weeks later. At 4-6 wk after their appearance, the tumors were disaggregated by collagenase, and 1×10^7 viable cells were injected sc into additional groups of normal or TXB recipients. The tumors were excised from the secondary hosts two weeks later, when they were weighed and their splenic indices calculated. Susceptibility of the TXB mice or of congenitally athymic nude mice to chemical carcinogenesis did not increase. However, once established, many tumors grew distinctly slower in the T cell-deficient animals. This was demonstrated to be due to lack of normal T cell function; tumors arising in TXB hosts progressed much faster in normal secondary hosts than in secondary TXB hosts. Three established methylcholanthrene-induced fibrosarcomas and two BALB/c fibrosarcomas (E4 and S3) from tissue culture also grew more slowly in T-deficient hosts in most cases. It is suggested that T cells may be required for immune surveillance, while the immune mechanism(s) that promote subsequent tumor growth are T cell-dependent. Alternative possibilities are discussed.

6937 LYMPHOCYTES T AND B IN LYMPHOPROLIFERATIVE SYNDROMES. (Fre.) Girard, J. P. (Hopital

Cantonal, CH-1200 Geneve, Switzerland); Fernandes, B. *Schweiz. Med. Wochenschr.* 105(37):1175-1179; 1975.

The existence of T and B lymphocyte markers has made it possible to define, at least roughly, some malignancies of the lymphocytic system in terms of their normal and tumoral constituents. The surface immunoglobulin markers not only make it possible to identify B lymphocytes but also to better define the concept of monoclonal proliferation of B cells by utilizing fluorescent antisera against the light chains K and lambda as well as the heavy chains. The notion of lymphoproliferative syndrome comprises a vast heterogeneous group of tumoral manifestations. In no case, except perhaps Burkitt's sarcoma, is the nature of the causative agent known. Although relations between malignant cells and normal lymphocytes are virtually unknown, a relation probably does exist since, in most cases, normal lymphocyte series are destroyed or suppressed by the spread of malignancy. Because of the importance of the interactions and cooperation between B and T lymphocytes, it can be assumed that when one of the two is deficient, the immune function cannot proceed in its totality. The authors also suggest that, as in the case of Hodgkin's disease and probably sarcoidosis, soluble elements from the cancerous cells have a cytotoxic effect on the normal cells, perhaps functioning as agents blocking specific lymphocytic receptors. Lymphocytic markers can, in certain cases, provide useful information on the stage of cellular division which marks the beginning of the tumoral proliferation.

- 6938 LEUKOCYTE ADHERENCE INHIBITION AND SPECIFIC IMMUNOREACTIVITY IN MALIGNANT MELANOMA. (Eng.) Halliday, W. J. (Dept. Microbiology, Univ. Queensland, Brisbane, Australia); Maluish, A. E.; Little, J. H.; Davis, N. C. *Int. J. Cancer* 16(4):645-658; 1975.

The leukocyte adherence inhibition (LAI) test was used to assess specific anti-tumor immunoreactivity in 80 patients with malignant melanoma, 21 of whom had apparently been successfully treated by surgery, and 44 control subjects. Reaction with melanoma extracts *in vivo* enabled the activity of blood leukocytes to be detected by inhibition of their adherence to glass, while serum was tested for factors that modified this inhibition. Of the patients with tumors (ranging from primary melanoma *in situ* to advanced disseminated disease), 22 of 24 had active leukocytes, and 50 of 58 had serum blocking factor; two of the sera, from patients with regressing tumors, were unblocking. After surgery with no clinical recurrence, leukocytes continued to be active except when tested several years after operation. Blocking factor rapidly disappeared in 16 of 20 patients tested, and in several patients examined serially the serum became unblocking. In three cases, persistence of serum blocking was followed by clinical diagnosis of metastases. Leukocyte activity was never detected in control subjects, 0 of 10, many of whom had other kinds of tumors or skin lesions. Blocking activity in serum was found in only 3 of 38 controls with no history of melanoma (one had

a fibrosing cellular blue nevus and two had liver disease). Thus, the LAI test correlates well with clinical and pathological findings, and shows great promise for the reliable, rapid and specific immunodiagnosis of malignant melanoma.

- 6939 BEHAVIOR OF LOCAL AND SYSTEMIC IMMUNOGLOBULINS IN PATIENTS WITH LUNG CANCER. (Eng.) Zermoski, J. (Medical Acad., Poznan, Poland); Gorny, M. K.; Wruk, M.; Sapula, J. *Int. Arch. Allergy Appl. Immunol.* 49(4):548-563; 1975.

Immunoglobulin (Ig) production in lung cancer patients was studied at both the local level (in the nearest primary tumor including the lymph node) and at the systemic level (in the serum). Tissue blocks from lung parenchyma in the vicinity of primary lung cancer and regional lymph nodes were collected during surgery from 22 patients. Cryostat sections were assessed for the presence of five immunoglobulin classes by means of immunofluorescence. Imprints made from surfaces of freshly resected tumors were used for indirect immunofluorescent reaction to detect anti-tumor antibodies in the autologous system sera of patients after surgery. Sera of 60 lung cancer patients were also assessed for IgG, IgA, and IgM levels. The direct vicinity of primary lung cancer and regional lymph nodes was a site of intensive immunoglobulin synthesis in plasma cells, with a predominance of the IgA and IgG classes. Serum anti-tumor antibody was found in three cases out of the 22 cases. There were significantly elevated serum immunoglobulin levels with IgA and IgG predominating. Inoperable patients had higher immunoglobulin levels than those who underwent surgery. The results indicate that immunoglobulin synthesis may be distinctly potentiated in the course of lung cancer, at least within three of the main classes tested.

- 6940 MYELOMA WITH PARAPROTEINEMIA IgD. (Cze.) Pola, V. (Vnitřní oddělení nemocnice, Pocatky, OÚNZ Pelhřimov, vedoucí MUDr. Vojtech Pola, II. vnitřní klinika lékařské fakulty Karlovy university, Hradec Králové, vedoucí doc. MUDr. J. Mazak, CSc.); Tichý, M. *Vnitř. Lek.* 21(3):269-273; 1975.

A 36-yr-old man with a pathological vertebral compression fracture was shown by immunoelectrophoretic analysis to have a serum paraprotein IgD concentration of 304 mg/100 ml and Bence-Jones protein in his urine. Rapid development of bone changes in the spine and humeral epiphyseal plate in the course of 2 months in the absence of any other basic systemic disorder suggested a quickly developing myeloma, although examination of the bone marrow showed no characteristic plasmacytes. Subsequent investigation revealed a picture typical for myeloma in the bones and bone marrow. This case represents the first description of myeloma with paraproteinemia IgD in the Czechoslovakian medical literature.

- 6941 AN ESTABLISHED BURKITT'S LYMPHOMA LINE WITH CELL MEMBRANE IgG. (Eng.) Klein, E. (Dep. Tumor Biol., Karolinska Inst., Stockholm, Sweden); Nilsson, K.; Yefenoff, E. *Clin. Immunol. Immunopathol.* 3(4):575-583; 1975.

The case report of a seven-yr-old female Burkitt patient whose biopsy of an ovarian tumor reacted with anti-IgG reagents and whose established lines maintained this reactivity is described. Seven independent cell lines were established, which morphologically resembled other cell lines derived from Burkitt's lymphoma tissue. The Ig production by biopsy cells was demonstrated by the labeled precipitation lines with anti-IgG and anti- κ reagents. Precipitation lines were also seen with anti-IgA and anti- κ reagents prior to the autoradiographic procedure; but since these were not labeled, IgA and κ chains were not produced by the cells *in vitro*. By the Mancini tests on supernatants from optimally growing cultures, the secretion and/or membrane turnover was 0.4-0.7 μ g IgG/ 10^6 cells/24 hr. Surface-localized IgG was detected by reactivity with anti- γ chain and anti-Fe reagents on the biopsy cells. A very weak reactivity with anti- κ reagent was also seen. Staining with Mutua serum revealed the expression of Epstein-Barr virus (EBV)-determined surface antigens. The reactivity with anti-Fe and the lack of reactivity with anti-IgM reagent seen on fixed smear were in good correspondence with the tests on viable cells. Staining was confined to the cell membrane and no cytoplasmic staining was distinguishable. Repeated examinations on the seven sublines performed by indirect immunofluorescence revealed reactivity with anti-IgG and anti- λ but not the anti-IgM reagent. The amount of IgG on the cultured line determined by hemmagglutination inhibition by IgG as reference was found in three independent tests to be 0.020, 0.012 and 0.013 μ g/ 10^6 cells. Membrane antigen and nuclear antigen were detected in the biopsy cells and in the cell lines. It is concluded that since well-defined characteristics of the biopsy cells were maintained in the cultures, they can be considered to represent the tumor cell population. Malignant transformation in Burkitt lymphoma is thus not restricted to IgM carrying lymphocytes.

- 6942 THE STRUCTURE OF AN IMMUNOGLOBULIN LIGHT CHAIN FRAGMENT IN MOUSE MYELOMA CELLS. (Eng.) Bridges, S. H. (Washington Univ. Sch. Medicine, St. Louis, Mo. 63110); Fleischman, J. B. *J. Mol. Biol.* 97(1):11-20; 1975.

An immunoglobulin light chain fragment, which forms a relatively large proportion of the radioactivity associated with intracellular immunologically precipitable immunoglobulin after short incubations with radioactively labeled amino acid was previously described in mouse myeloma cells. A detailed characterization of this fragment from S176 and J558 mouse myeloma cells was undertaken, including purification and subsequent peptide mapping, in order to determine the possible significance of this fragment in the biosynthesis of the complete light chain. The

purified material appeared heterogeneous in length on 15% sodium dodecyl sulfate-polyacrylamide gel electrophoresis, with a modal molecular weight of 15,500. Peptide mapping of [3 H]leucine-labeled material, with homologous light chain carrier, demonstrated that both variable and constant region peptides were present. These data, and the pattern of specific activity derived from the maps, are more compatible with the fragment being a collection of nascent chains and/or proteolytic fragments than a discrete variable region piece.

- 6943 DETECTION OF A POSSIBLE PRECURSOR OF IMMUNOGLOBULIN LIGHT CHAIN IN MOPC 41A PLASMACYTOMA CELLS. (Eng.) Schmeckpeper, B. J. (Royal Melbourne Hosp., Victoria, 3050, Australia); Adams, J. M.; Harris, A. W. *FEBS Lett.* 53(1):95-98; 1975.

A possible precursor, a polypeptide which appears to be equivalent to the P chain made in cell-free systems, of immunoglobulin light chain in MOPC 41A plasmacytoma cells was detected in the presence of an inhibitor of proteolytic enzymes. In initial attempts to detect intracellular P chain, no immunoprecipitable polypeptide the size of the MOPC 41A P chain was found in [35 S]methionine-labeled MOPC 41A cells analyzed by SDS gel electrophoresis, suggesting that if intracellular P chain exists it must be short lived. However, when the plasmacytoma cells were incubated for 30 min with [35 S]methionine in the presence of a protease inhibitor, a new polypeptide was detected. The cells incubated with TLCK (50, 125, or 250 μ g/ml of N- α -tosyl-L-lysyl chloromethane hydrochloride) yielded a polypeptide which had the same mobility as the reference MOPC 41A P chain and which was precipitable by anti- κ serum. At 250 μ g/ml TLCK, there was twice as much of this polypeptide as there was the light chain. However, the new polypeptide was detected only when TLCK was present during the incorporation of [35 S]methionine. TLCK was the only inhibitor tested which consistently revealed the new polypeptide: it was not detected with P-toluene sulphonyl-L-arginine methyl ester hydrochloride and only found in one of two experiments with tosyl-L-phenylalanylchloromethane. No immunoprecipitable polypeptide with the mobility of P chain was detected in four other plasmacytoma cell lines: P3K, MPC 11, HPC-108, or MOPC 315. Thus, this demonstration of an intracellular P chain supports the argument that the polypeptide formed in the cell-free system is not an artifact and that the P chain is a biosynthetic precursor to the light chain.

- 6944 COMPARATIVE STUDIES ON MONOTYPIC IgM λ AND IgG κ FROM AN INDIVIDUAL PATIENT. I. EVIDENCE FOR SHARED V_H IDIOTYPIC DETERMINANTS. (Eng.) Hopper, J. E. (Pritzker Sch. Medicine, Univ. of Chicago, Chicago, Ill. 60637). *J. Immunol.* 115(4):1101-1107; 1975.

A comparative idiotypic antigenic analysis was made of an IgM λ and IgG κ paraprotein obtained from sera of an individual patient, Br, with malignant lymphoma

(Waldenstrom's type). The analysis revealed the presence of very similar idiotypic determinants associated with the V_H regions of the Br μ - and γ -chains. In addition, the IgGk protein expressed light (L) chain-associated idiotypic determinants which were not evident on the IgM λ protein or its isolated L chains. This extensive idiotypic antigenic analysis showed that the BrIgM λ and BrIgGk paraproteins share very similar V_H idiotypic determinants. These determinants, however, could not be detected in relatively large amounts of heterologous nonspecific or monoclonal IgG and IgM, nor on Ig molecules contained in a large number of normal and myeloma sera.

- 6945 CHARACTERISTICS OF THE EFFECTOR CELL MEDIATING CYTOTOXICITY AGAINST ANTIBODY-COATED TARGET CELLS: I. PHAGOCYTIC AND NON-PHAGOCYTIC EFFECTOR CELL ACTIVITY AGAINST ERYTHROCYTE AND TUMOUR TARGET CELLS IN A ^{51}Cr RELEASE CYTOTOXICITY ASSAY AND [^{125}I]IUdR GROWTH INHIBITION ASSAY. (Eng.) Greenberg, A. H. (Manitoba Inst. Cell Biology, 700 Bannatyne Ave., Winnipeg, Manitoba, Canada R3E 0V9); Shen, L.; Medley, G. *Immunology* 29(4):719-729; 1975.

The susceptibilities of SRBC and two different mouse tumor target cells to antibody-dependent cell-mediated cytotoxicity by well characterized phagocytic and non-phagocytic spleen cell populations were compared. BALB/c spleen cell preparations were tested with and without removal of phagocytic cells by the carbonyl iron method. The antisera consisted of rabbit anti-SRBC antiserum and C3H (H-2^K) anti-P-815-Y (H-2^d) antiserum. The target cells were SRBC, cultured mouse P-815-Y mastocytoma, and cultured mouse SL2 lymphoma. For phagocytosis assays, erythrocyte-antibody-complement (EAC) complexes were prepared by coating ^{51}Cr -labeled SRBC with rabbit anti sheep hemolysin and mouse complement; spleen cells were then mixed with the EAC in a ratio of 1:5, followed by incubation and final measurement of radioactivity of sedimentable non-lysed cells. For cytotoxicity assays using SRBC or tumor cells as target cells, spleen cells and appropriate antibody were incubated with ^{51}Cr -labeled target cells and radioactivity was measured in the supernatants of sedimented, non-lysed cells. For the growth inhibition assay, P-815-Y or SL2 tumor cells were first incubated with spleen cells and C3H anti-P-815-Y serum; the incubation mixture was then incubated with (^{125}I) iododeoxyuridine (IUdR); finally, uptake of radioactivity was measured. Both phagocytic and nonphagocytic spleen cell preparations were able to destroy rabbit antibody-coated SRBC in the ^{51}Cr release assay, while only nonphagocytic cells were active against C3H anti-P-815-Y-coated SL2 lymphoma cells. In contrast to the coated SL2 cells, anti-P-815-Y-coated P-815-Y mastocytoma cells were not susceptible to spleen cells in the ^{51}Cr release assay; however, they were markedly inhibited in their uptake of (^{125}I)IUdR in the growth assay. It appeared that the effects of non-immune spleen cells on antibody-coated tumors may

be of two types, namely, inhibition of growth (cytotoxicity) and direct membrane damage leading to cell death. The two phenomena were demonstrated to be independent of one another in that the P-815-Y tumor cells could be inhibited from incorporating (^{125}I)IUdR while failing to release ^{51}Cr , using the same antibody and spleen cell population. Based on the postulate that a membrane event in phase G₁ commits tumor cells to a reversible inhibition of cell division, it appeared possible that the observed spleen cell-target cell interaction which resulted in cessation of tumor cell occurred through a similar membrane signal without the concomitant membrane damage which would have resulted in ^{51}Cr release. It was concluded that not all tumors are susceptible to damage detectable by ^{51}Cr release and not all antibodies are capable of inducing killing in this type of assay, but that at the same time spleen cell activity can be detected in a growth inhibition assay.

- 6946 PRESENCE OF CHICKEN CELL SURFACE ANTIGEN ON ROUS VIRUS ACTIVATED IN HETEROKARYONS OF TRANSFORMED NON-PERMISSIVE HAMSTER CELLS AND CHICKEN CELLS. (Eng.) Vigier, P. (Institut du Radium, Faculte des Sciences, 91-Orsay, France); Aupoix, M. *J. Gen. Virol.* 28(2):265-269, 1975.

The presence of host cell surface antigen (HCSA, chicken cell surface antigen) on the virus envelope produced by heterokaryons formed, in the presence of inactivated Sendai virus, by chick embryo (CE) cells and cells of a subclone (Rous sarcoma, RS2/3), derived from the RS₂ clone obtained by transforming BHK21/C13 hamster cells with SR-Rous sarcoma virus-D (RSV-D), was investigated. Mixed cultures of RS2/3 and CE cells after Sendai-virus-mediated fusion were exposed to γ rays (3,000 R) to obtain only early RSV from heterokaryons by preventing secondary infection of nonfused CE cells. Two methods of cell fusion were used in two separate experiments; 3 x 10⁷ trypsinized RS2/3 cells were irradiated (5,000 R) with [^{60}Co]- γ rays and mixed with either (a) 15 x 10⁷ cells, and then plated, fused with UV-irradiated Sendai virus and irradiated immediately with 3,000 R; or (b) 9 x 10⁷ CE cells, and then pelleted by low speed sedimentation, fused 20 hr later with inactivated Sendai virus, and irradiated with 3,000 R. Samples of concentrated virus were then incubated with anti-CE rabbit serum plus complement and assayed by the focus assay. The virus produced in both experiments was inactivated only by anti-CE complement, indicating that it must carry HCSA on its envelope, but no RS₂ cell surface antigen. The degree of inactivation by anti-CE serum and virus complement produced by heterokaryons in irradiated cultures was lower (5% survival against 1-3%) than the degree of inactivation of virus produced by CE-cells; however, the significance of this difference is doubtful. The results indicate that activated RSV must mature and bud at chicken-specific sites of the heterokaryon surface. The presence of HCSA may account for the high virus production of CE cells, but may not be an absolute prerequisite for virus maturation and release.

6947 NEUTROPHIL-MEDIATED TUMOR CELL CYTOTOXICITY:
ROLE OF THE PEROXIDASE SYSTEM. (Eng.)

Clark, R. A. (Dep. Med. Microbiol., Univ. Washington, Seattle); Klebanoff, S. J. *J. Exp. Med.* 141(6):1442-1447; 1975.

The ability of human polymorphonuclear leukocytes (PMN) to act as effector cells against mammalian tumor cells was studied in two cytotoxicity assays. In the first assay, cells of an ascitic Moloney virus-induced lymphoma maintained in BALB/c mice were labeled with ^{51}Cr -chromate and release of label was determined in a cytotoxicity system comprising PMN, preopsonized zymosan, and a halide. In the second assay, tumor development was compared in BALB/c mice injected in the peritoneal cavity with either untreated lymphoma cells or cells incubated for two hours with the components of the cytotoxicity system. In the PMN-zymosan-halide system, significant ^{51}Cr release above control occurred using either 0.1 M chloride or 10^{-4} iodide as the halide. Cytotoxicity was abolished by deletion of each component of the system; by pretreating the PMN with heat, homogenization or sonication; or by the use of nonopsonized zymosan. A cytotoxic effect was present at an effector-to-target cell ratio of 1.25:1. Only six of 25 mice receiving tumor cells exposed to the complete toxicity system developed tumors, compared with 22 of 24 animals receiving control cells. Omission of PMN, zymosan, or both halides resulted in tumors in 6 of 6, 6 of 6, and 5 of 6 animals, respectively. Azide, cyanide, and catalase inhibited the cytotoxic effect of PMN, suggesting that this effect was mediated by myeloperoxidase (MPO) and H_2O_2 . Subsequent experiments showed that PMN from a patient with hereditary MPO deficiency and six patients with defective H_2O_2 production (WBC glucose-6-phosphate deficiency and chronic granulomatous disease of childhood) were not cytotoxic; however, activity was restored by the addition of purified MPO (16 mU) and H_2O_2 ($5 \times 10^{-5}\text{M}$), respectively. The findings support the hypothesis of a mechanism involving the phagocytosis-induced extracellular release of MPO and H_2O_2 and their reaction with a halide cofactor to damage the target cells.

6948 AUTOGENOUS IMMUNITY TO ENDOGENOUS RNA TUMOR VIRUS: REACTIVITY OF NATURAL IMMUNE SERA TO ANTIGENIC DETERMINANTS OF SEVERAL BIOLOGICALLY DISTINCT MURINE LEUKEMIA VIRUSES. (Eng.)

Lee, J. C. (Frederick Cancer Res. Center, P.O. Box B, Frederick, Md. 21701); Ihle, J. N. *J. Natl. Cancer Inst.* 55(4):831-838; 1975.

Sera from normal (C57BL/6 X C3H/Anf) F_1 (B6C3F $_1$) mice reacted with several biologically distinct murine leukemia virus(es) (MuLV) by radioimmune precipitation assays which used purified tritiated leucine-labeled virus. The reactivities of this natural antibody to viral envelope antigens of two laboratory strains (Rauscher and Moloney) and two endogenous mouse C-type viruses (AKR and BALB:virus-2) were further analyzed and compared by sodium dodecyl sulfate polyacrylamide gel electrophoresis.

Similar patterns of antibody reactivities to AKR MuLV and the two member viruses of the Friend-Moloney-Rauscher group were found. Three major antigenic determinants of the virus envelope, gp71, gp43, and p15, were recognized by and precipitated natural antibody. In all viruses examined, normal B6C3F $_1$ sera precipitated comparable amounts of gp71 and gp43. Compared with the other viruses, the amount of p15 (relative to the glycoproteins) precipitating from BALB:virus-2 was significantly lower. This appears to be due to a lesser amount of p15 on the xenotropic virus. While heterologous antisera to purified gp71 and p15 of MuLV reacted to a certain degree with rhabdomyosarcoma virus 114 and rat leukemia virus, natural mouse antibody did not. These results suggest that MuLV have common antigenic determinants recognized by natural antibody, and that the reactivities of natural antibody in an autogenous immune response are restrictive in contrast to immune antibody produced in a heterologous host. The most significant observation was that the antigenic determinants recognized by normal B6C3F $_1$ sera were similar for several MuLV isolates.

6949 CELL-MEDIATED IMMUNITY TO MOLONEY SARCOMA VIRUS IN MICE. I. ANALYSIS OF ANTIGENS RESPONSIBLE FOR LYMPHOCYTE STIMULATION IN REGRESSOR MICE. (Eng.) Knight, R. A. (ICRF Tumour Immunology Unit, University Coll. London, London WC1E 6BT, England); Gorczynski, R. M. *Int. J. Cancer* 15(1):48-58; 1975.

Purified viruses, viral antigens, and cell extracts were tested for their ability to stimulate protein synthesis by the Moloney pseudo-type of Moloney mouse sarcoma virus (MSV-M) regressor spleen cells from BALB/c mice. Immune, but not normal cells, responded to MSV-M, but not to the Gross pseudo-type of Moloney mouse sarcoma virus (MSV-G) virus, and to the type-specific viral envelope glycoprotein from MSV-M virus. Extracts of mouse embryo fibroblasts transformed by either MSV-M or MSV-G, however, specifically stimulated MSV-M regressor spleen cells. Cells stimulated by different antigens, and by phytohemagglutinin, had the same sedimentation profile and were identified as T-lymphocytes.

6950 DISTRIBUTION AND ANTIBODY-INDUCED REDISTRIBUTION OF A MAMMARY TUMOR VIRUS-INDUCED AND A NORMAL ANTIGEN ON THE SURFACE OF MOUSE LEUKEMIA CELLS. (Eng.) Hilgers, J. (Netherlands Cancer Inst., 108 Sarphatistraat, Amsterdam-1004, Netherlands); van Blitterswijk, W. J.; Bont, W. S.; Theuns, G. J.; Nusse, R.; Haverman, J.; Emmelot, P. *J. Natl. Cancer Inst.* 54(6):1335-1342; 1975.

With the indirect membrane immunofluorescence test, the distribution and antibody-induced redistribution (patching and capping) of a mammary tumor-virus-induced (MLr) and a normal (Thy 1.2) cell-surface antigen were compared on GR mouse thymocytes and leukemia cells (GRSL2). AKR mice were immunized with

thymocytes from C3Hf mice to produce antiserum against Thy 1.2. At 0°C Thy 1.2 fluorescence was ringlike and more intense on GRSL2 cells than on thymocytes, whereas MLr fluorescence on GRSL2 cells was patchlike and brighter than Thy 1.2 fluorescence. At 20 or 37°C, capping of Thy 1.2 on both cell types was readily achieved but MLr capping occurred only in a few GRSL2 cells and was less pronounced. However, after addition of the secondary antibodies, MLr capping was markedly increased by gradual cooling of cells to about 17°C. Conversely, after addition of antibodies at 0°C, gradual warming of cells under the fluorescence microscope resulted in extensive capping both of MLr and Thy 1.2 at 13-14°C. Rapid cooling or rapid warming led to almost instantaneous capping. These results may be explained by the occurrence of phase transitions or phase separations in the lipid domain of the plasma membranes, within the particular temperature range. Thy 1.2 caps were small and eventually were endocytosed, whereas the MLr caps were large and were exfoliated from the cells.

- 6951 DYNAMIC ALTERATIONS IN SOME SURFACE PROPERTIES OF FRESHLY EXPLANTED MOLONEY LYMPHOMA CELLS. (Eng.) Ran, M. (Dr. Geroge S. Wise Life Sciences Center, Tel Aviv Univ., Tel Aviv, Israel); Eshel, I.; Witz, I. P.; Klein, G. *J. Natl. Cancer Inst.* 55(4):843-849; 1975.

The effects of the surface properties of explanted tumor cells (Moloney virus-induced lymphoma YAC) on the properties of antibodies to these cells were studied. When YAC cells were freshly explanted into culture two events occurred in the first 2 hr. The cells lost their natural IgG coat, and their sensitivity to complement-dependent lysis (CdL) mediated by antibodies to Moloney lymphoma cells decreased or increased. An increasing sensitivity to CdL as a function of incubation time at 37°C occurred when the sensitivity to CdL was low at explantation. A decreasing sensitivity to CdL was probable in instances of a high sensitivity to CdL at explantation. Explantation always caused loss of the Ig coat. Artificial coating of YAC cells with antibodies to Moloney lymphoma immediately after explantation moderated the alterations in their sensitivity to CdL. This occurred even though a functional antibody did not remain on the cells as evidenced from the gradually decreased sensitivity of the artificially coated cells to the addition of complement. Spent culture media in which freshly explanted cells grew for 60 to 120 min sometimes blocked CdL of YAC cells mediated by antibodies to Moloney lymphoma.

- 6952 INHIBITION OF *IN VITRO* GROWTH OF LYMPHOMA CELLS BY MACROPHAGES FROM TUMOR-BEARING MICE. (Eng.) Kirchner, H. (Natl. Cancer Inst., Bethesda, Md. 20014); Holden, H. T.; Herberman, R. B. *J. Natl. Cancer Inst.* 55(4):971-975; 1975.

The specificity of a growth inhibiting activity of spleen cells was studied. Spleen cells from C57BL/6 mice bearing primary tumors induced by the Moloney

strain of murine sarcoma virus (MuSV) strongly inhibited the uptake of tritiated thymidine (^3H -TDR) by RBL-5 lymphoma cells in a 48-hr growth-inhibition assay (GIA). This activity was first detected seven days after MuSV was injected; it peaked at 14 days, and was usually no longer detectable after 18-21 days. It could be detected at effector cell/target cell ratios between 20:1 and 5:1, at which normal spleen cells had a growth-promoting effect. The effector cells in the GIA were not T cells, and various depletion experiments suggested that they were macrophages. Macrophages of a purity of over 95% were obtained in the glass-adherent fraction of thioglycollate-induced peritoneal exudate cells (PEC). PEC were growth inhibitory when obtained from either normal or MuSV tumor-bearing mice. However, at effector cell/target ratios of 2.5:1, only PEC from MuSV tumor-bearing mice had an effect. Activity of spleen cells in the GIA appeared distinct from T-cell-dependent specific cytotoxicity, which was not affected by removal of macrophages. Activity in the GIA was nonspecific, and target cells which do not cross-react with RBL-5 cells were equally inhibited. Further, spleen cells from mice bearing primary tumors induced by 3-methylcholanthrene were also fully active against RBL-5 cells. Supernatants from spleen cell cultures obtained from mice 14 days post-injection with MuSV also inhibited the incorporation of ^3H -TDR by RBL-5 cells *in vitro*. However, this effect seemed to be an artifact, since the tumor cells proliferated equally well in the presence or absence of the supernatants. In contrast, the direct effect of spleen cells from MuSV tumor-bearing mice was reflected both by an inhibition of cell proliferation and by inhibition of ^3H -TDR incorporation.

- 6953 ACTIVATION OF "ECLIPSED" LYMPHOID CELLS FROM ADVANCED TUMOR-BEARING MICE THROUGH ADOPTIVE TRANSFER TO SUBLETHALLY IRRADIATED SYNGENEIC HOSTS. (Eng.) Youn, J. K. (Tissue Culture and Virology Lab., E.R.C.N.R.S. No. 38, Institut Gustave-Roussy, 94800 Villejuif, France); Le Francois, D.; Hue, G.; Santillana, M.; Barski, G. *Int. J. Cancer* 16(4):629-638; 1975.

Immunologically inactive or "eclipsed" lymphoid cells from advanced tumor-bearing mice were investigated following their adoptive transfer to irradiated syngeneic hosts. Experiments were performed with two syngeneic tumor-host systems: the T5-BALB/c tumor line chronically infected with a low-leukemogenic Rauscher virus variant and the TML-C3H tumor line developed from a spontaneous C3H/He mouse mammary tumor. Peritoneal cells (PC) from advanced tumor-bearing mice eclipsed peritoneal cells (EPC) appeared to have lost any capacity to inhibit specifically the growth of corresponding tumor target cells *in vitro* colony inhibition (CI) tests, whereas PC from immunized mice (IPC) were perfectly active. When these EPC were adoptively transferred by intraperitoneal inoculation into sublethally irradiated (450 R) syngeneic mice in association with respective tumor extracts (TE), the PC from such recipient mice, taken 5 to 13 days

later, were nearly as active in *in vitro* CI tests as were PC from parallel IPC-recipient mice. For this recovery of specific immunological activity following the adoptive transfer of EPC, the adjunction of the TE and irradiation of the recipient animals may be necessary. No specific immunological activity was seen in PC from irradiated mice to which PC from normal mice had been transferred with TE. An effect of adoptive transfer of EPC (retardation of tumor growth) was also observed *in vivo*. The "elipsed" immunologically inactive state of the EPC in mice bearing advanced tumor is not irreversible. In 3 experiments using a total of 57 mice, adoptive transfer of EPC from advanced-tumor bearing mice into sublethally irradiated, syngeneic mice caused significant resistance to a tumor challenge.

- 6954 CELL-MEDIATED IMMUNITY TO EPSTEIN-BARR-VIRUS-TRANSFORMED LYMPHOBLASTOID CELLS IN ACUTE INFECTIOUS MONONUCLEOSIS. (Eng.) Royston, I. (Stanford Univ. Medical Center, Stanford, Calif. 94305); Sullivan, J. L.; Periman, P. O.; Perlin, E. *N. Engl. J. Med.* 293(23):1159-1163; 1975.

Mononuclear peripheral blood WBC from 21 patients (9 men, 15 women, 14-28 yr-old) with infectious mononucleosis and 16 healthy controls were tested in a ^{51}Cr -release assay for cytotoxicity against two human lymphoblastoid cell lines derived from the same donor. One line contained the Epstein-Barr virus (EBV); the other did not. Acute-phase WBC were significantly more cytotoxic against the EBV-infected cell line than were control WBC. Mean lysis at a WBC-target-cell ratio of 100:1 was 10.6% for patients and 3.4% for controls ($P < 0.0005$). Cytotoxicity correlated with the percentage of atypical lymphocytes. Cells of three patients with acute mononucleosis-like illnesses failed to show killing activity above those of normal controls. Cytotoxicity against the EBV-negative line was not significantly different for each group. The finding of cytotoxic cells in infectious-mononucleosis patients with atypical lymphocytes suggests that these cells operate *in vivo* to limit the proliferation of altered EBV-transformed B lymphoblasts.

- 6955 COMPARISON OF INTRACITOPLASMIC A PARTICLES AND INTRACISTERNAL A PARTICLES. (Eng.) Wivel, N. A. (Natl. Cancer Inst., Bethesda, Md. 20014); Smith, G. H.; Ozer, H. L. *Int. J. Cancer* 16(2):240-248; 1975.

To test the relationship between intracytoplasmic A particles (CAP) and intracisternal A particles (IAP), comparisons were made of antigens and of structural proteins of preparations of particles from the two different sources. IAP were purified from the MOPC-104E plasma cell tumor, while CAP were purified from transplantable Leydig cell tumors and from spontaneous mouse mammary tumors. Mouse mammary tumor virus (MMTV) used in the stu-

dies was purified from C3H mouse milk or from C3H/He mammary tumors. Antisera against the three different antigens were raised in rabbits. In double diffusion tests, IAP would react against IAP antisera only after solubilization with sodium dodecyl sulfate (SDS) and mercaptoethanol. In complement fixation tests, cross-reactivity of IAP antiserum with CAP particles was slight and even less with MMTV. Cross-reactivity of CAP antiserum was lacking with IAP protein, but was strong with MMTV, presumably reflecting the presence of common viral proteins. In double diffusion, CAP antiserum produced two precipitin lines with CAP, with one line showing identity with an antigen in IAP. The CAP antiserum did not, however, react with a partially purified major structural protein of IAP. MMTV antisera showed by double diffusion at least one antigen in common between CAP and MMTV. The antigenic cross-reactions did not, therefore, appear to involve the major structural protein of IAP, but may have reflected the presence of common antigenic determinants located on minor proteins. SDS-polyacrylamide gel patterns for the two types of A particles showed distinct differences. Major polypeptide constituents of CAP had molecular weights of 82,000, 37,000, and 18,000, while those of IAP had molecular weights of 73,000, 49,000, and 32,000. Electron microscopy revealed such ultrastructural details as the wider range of diameters in IAP, the lack of outer shell in CAP, and the greater average central space in CAP. It was concluded that there were no apparent major similarities between IAP and CAP.

- 6956 EFFECT OF IMMUNOSUPPRESSION AND IMMUNE STIMULATION ON ONCOGENIC-VIRUS ACTIVATION. (Eng.) Wood, M. L. (Cancer Res. Inst., 185 Pilgrim Road, Boston, Mass. 02215); Hirsch, M. S.; Black, P.; Monaco, A. P. *Transplant. Proc.* 7(1/Suppl.1):499-503; 1975.

A mouse model was employed in a series of experiments to study the influence of chronic immunosuppression and/or persistent immunostimulation by foreign histocompatibility antigens on the activation of murine leukemia virus. BALB/c mice (H-2^d) were divided into four groups: group A received no treatment, group B was grafted with either A/J (H-2^k) or DBA/2 (H-2^b) skin, group C received anti-lymphocyte serum (ALS, 0.25 ml ip twice weekly for 2 wk and 0.1 ml twice weekly for 2 wk), and group D received both a skin graft and ALS treatment. Twelve percent of group A were positive for C-type leukemia virus, as were 10% of the mice with A/J grafts, 36% of group C, and 54% and 69% of group D mice receiving A/J or DBA/2 skin grafts, respectively. None of the mice receiving only DBA/2 grafts were positive. In a second experiment, 50% of mice grafted with A/J skin receiving high doses of ALS (0.2 ml ip daily) and 50% of A/J skin grafted mice receiving ALS burst therapy (0.2 ml ip on day 4, 5, and 6 each wk following grafting) were virus positive. Only 10% of A/J skin grafted mice receiving a low-dose regimen ALS (0.1 ml ip every 5 days) were virus-positive. In another experiment, 36 DALB/c mice grafted with A/J skin were divided

into two groups: one receiving 0.25 ml ip ALS twice weekly and the second group was untreated. Virus was detected in the spleens and lymph nodes 7 to 10 days after grafting and persisted in mice receiving ALS. In a fourth experiment, the authors found that various immunosuppressive protocols differed in their ability to prolong DBA/2 skin grafts. The normal MST was 14.8 days; 75% of ALS-treated (0.2 ml twice weekly) and 45% of high-dose cyclophosphamide (20 mg/kg daily) had mice with surviving grafts by day 28. These studies indicate that virus activation occurs in immunosuppressed BALB/c mice after immunostimulation by skin grafting. The authors suggest that prolonged graft survival due to effective immunosuppression exposes the host to a period of immunostimulation by histocompatibility antigens, resulting in virus activation.

- 6957 MEMBRANE MOBILITY AGENT ALTERS THE CONSEQUENCES OF LECTIN-CELL INTERACTION IN A MALIGNANT CELL MEMBRANE. (Eng.) Lustig, S. (Dept. Life Sciences, Bar-Ilan Univ., Ramat-Gan, Israel); Pluznik, D. H.; Kosower, N. S.; Kosower, E. M. *Biochim. Biophys. Acta* 401(3):458-467; 1975.

To clarify the relationship between membrane site mobility and agglutinability, a study was made on the effect of a membrane mobility agent, 2-(2-methoxyethoxy)-ethyl 8-(*cis*-2-*n*-octylcyclopropyl)-octanoate (A₂C) on the interaction between wheat germ agglutinin and P-815-X2 mastocytoma cells. A₂C, dispersed in phosphate-buffered saline by sonication just before use, was added in varying concentrations to suspended tumor cells at 5 x 10⁶ cells/ml, the mixture was incubated 30 min at 24 C, wheat germ agglutinin (unlabeled or fluorescein-labeled) at a final concentration of 10 µg/ml was added for an additional incubation at 4 C or 37 C, and aliquots were withdrawn at various time intervals for determination of extent of agglutination, distribution of labeled agglutinin bound to cell surface, and cytotoxicity. Extent of agglutination was determined on the basis of the number of cells which were not agglutinated out of the total number of cells present in a control sample incubated without lectin. The distribution of labeled agglutinin on the cells was observed with a fluorescence microscope. Cytotoxicity was determined by counting cells in 0.4% trypan blue solution. In samples treated with agglutinin, counting was performed after disaggregation of cell agglutinates to single cells by addition of 0.3 M N-acetyl-D-glucosamine. The results showed that the membrane mobility agent, A₂C, promoted a redistribution of lectin-membrane site complexes, a cap-like arrangement forming in place of the diffuse arrangement observed in the absence of the agent. The membrane mobility agent simultaneously diminished the degree of agglutination by the lectin and, in addition, increased the sensitivity of interphase cells to the cytolytic effect of the agglutinin. It was noted that the cap formation promoted by A₂C or any other mobility process which permits accumulation of sites in a restricted area of a membrane might well be expected to diminish the probability of multiple bridge formation between cells.

- 6958 BINDING OF ¹²⁵I-CONCAVALIN A AND AGGLUTINATION OF EMBRYONIC NEURAL RETINA CELLS: AGE-DEPENDENT AND EXPERIMENTAL CHANGES. (Eng.) Martinozzi, M. (Inst. Histology and General Embryology, Univ. Rome, Rome, Italy); Moscona, A. A. *Exp. Cell Res.* 94(2):253-266; 1975.

The finding that embryonic chick neural retina cells dissociate from retina tissue by treatment with ethylene bis-(oxyethylene nitrilo)tetraacetic acid (EGTA, a calcium chelator) and show an age-dependent decline in ability to agglutinate with concanavalin A (Con A) led to an investigation into the nature of this decline. Mature retina cells could be rendered agglutinable by mild trypsinization; thus, this developmental change in cell surface properties is not due to the loss of Con A binding sites. It is also not due to masking of Con A receptors, or to a decrease in their amount, since retina cells from late embryos (19 days) bound four times as much ¹²⁵I-Con A as cells from early embryos (eight days). These findings lead to the suggestion that, as the retina differentiates, the lateral mobility of Con A receptors in the cell membrane decreases resulting in a reduction of cell agglutinability; trypsinization of late embryo retina cells increases the mobility of the receptors and thereby facilitates their clustering by the lectin into a configuration conducive to cell agglutination. The ability of late embryo (19 day) retina cells dispersed with EGTA to agglutinate with Con A (25 µg/ml) could be increased by still other treatments: by preincubation of the cell suspension in Tyrode's balanced salt solution (one hour, 37 C); and by brief pre-exposure to 2.5% glutaraldehyde. These two treatments did not enhance cell agglutination with wheat germ agglutinin (WGA, 50 µg/ml). Glutaraldehyde treatment of trypsinized cells made them agglutinable with Con A also at 4 C; cells treated otherwise agglutinated only at higher temperatures. Surface-saturation of monodispersed retina cells with Con A at 37 C--but not at 4 C--prevented their agglutination with this lectin, but not with WGA; this inhibition was reversible by methyl α-D-glucopyranoside (10 mg/ml).

- 6959 A SCREENING METHOD TO DETECT CLONAL SECRETION OF DNP-SPECIFIC ANTIBODY. (Eng.) Waring, G. L. (Dept. Zoology, Indiana Univ., Bloomington, Indiana 47401). *J. Cell. Physiol.* 86(2/ Suppl. 1/Part II):389-401; 1975.

Spontaneous variants of the IgA immunoglobulin secreting mouse myeloma, S194-2, were isolated by cloning the line on soft agar and screening for the loss of secreted S194 immunoglobulin. Because S194 IgA possesses dinitrophenol (DNP) binding activity, the screening method was designed to test for clonal secretion of antibody which specifically precipitated DNP-ferritin conjugates. Precipitates formed over IgA secreting S194 clones, whereas none were evident over nonsecreting XCl clones nor IgG secreting MOPC 21 clones (MOPC 21 IgG does not bind DNP). In addition, the method was sensitive to the amount of immunoglobulin secreted. By continual selection of exceptionally reactive clones with this assay, a S194 culture was obtained which secreted

5-6 times as much IgA as the original mass culture. Spontaneous variants were isolated from six independent subclones of this parent line with an overall frequency estimated at 2.7×10^{-5} per cell per generation. Biochemical analysis of these variants showed that all secreted reduced or undetectable amounts of IgA. No variants were obtained that secreted IgA molecules altered at the DNP binding site, or that secreted immunoglobulin subunits alone. Variants of the latter class have, however, been obtained in high frequency in other myeloma strains by other investigators.

- 6960 ANOMALOUS REACTIONS OF MOUSE ALLOANTISERA WITH CULTURED TUMOR CELLS. I. DEMONSTRATION OF WIDESPREAD OCCURRENCE USING REFERENCE TYPING SERA. (Eng.) Klein, P. A. (Coll. Medicine, Univ. Florida, Gainesville, Fla. 32610). *J. Immunol.* 115(5):1254-1260; 1975.

The distribution of anomalous anti-tumor antibodies (AAA) and their effects on measurement of alloantigenic specificities is reported. Mouse alloantisera produced against different specificities of the K, I, and D regions of the H-2 gene complex revealed anomalous AAA when tested on cultured 20-methylcholanthrene (MCA) induced sarcoma cells from C57BL/10SgSn H-2 congenic mice. Absorption experiments demonstrated that the anomalous activity in these sera was directed against a tumor membrane antigen which was distinct from H-2 region specificities against which the reference alloantisera were produced, and which was shared by many cultured sarcoma lines. Similar anti-tumor antibody activity could be demonstrated in the serum of older (> 12 weeks) but not younger normal unimmunized mice of the strains used as recipients for alloantiserum production. The observed AAA activity in these alloantisera may be due to the presence of antibodies reactive with envelope antigens of murine leukemia virus which are expressed on sarcoma cells maintained in culture. These results in mice resemble observations of anomalous antibodies in HL-A typing sera in humans. These AAA can lead to errors in measurement of H-2 and HL-A specificities on tumor cells.

- 6961 TRANSPLANTATION BEHAVIOR OF ALLOTRANSPLANTABLE TUMOR LINES DERIVED FROM IMMUNOLOGICALLY MODIFIED HOSTS. (Eng.) Parks, R. C. (American Medical Center at Denver, Spivak, Colo. 80214); Jacobs, B. B. *J. Natl. Cancer Inst.* 54(5):1079-1083; 1975.

The effects of immunologic modifications on the successful transplantation of an *in vitro*-derived allotransplantable strain-specific line of the BALB/c testicular tumor C4092 were studied in inbred DBA/1 ($H-2^d$), BALB/c ($H-2^b$), C57BL/6 ($H-2^b$), A/Bi ($H-2^a$) and Swiss mice. Five methods of pretreatment were used to condition the recipients of the tumor allografts: neonatal thymectomy, immunologic enhancement, rabbit antimouse serum treatment, sublethal x-irradiation, and immunization with mitomycin C-

inactivated C4092 tumor cells. The C4092 tumor was conditioned to grow in H-2 incompatible DBA/1 mice by prior maintenance *in vitro* as an organ culture explant. It was then serially transplanted successfully in untreated DBA/1 mice. Tumors derived from conditioned DBA/1 mice always grew in syngeneic BALB/c mice; however, one passage in BALB/c mice resulted in either a lost or a greatly reduced ability to grow in untreated DBA/1 mice. *In vivo* and *in vitro*-modified tumors differed in degree of transplantability and in the stability of immunogenic changes. The mice bearing allotransplantable tumors derived by these methods showed similar immunologic characteristics, i.e. impaired rejection of both nonmodified BALB/c tumor and BALB/c skin grafts and normal or increased spleen reactivity in graft-versus-host reaction assays. Because of these similarities, it is concluded that adaptations of both host and graft contribute to graft survival. The authors suggest that modifications similar to those reported here may contribute to survival of spontaneous tumors in the presence of tumor-associated transplantation antigens. Exploitation of the induced modification in both graft and host that favored both survival of the allograft in the organ transplant recipient and rejection of the tumor by the cancer patient therefore would appear to be a reasonable goal.

- 6962 MODULATION OF GvH PROLIFERATION BY CYCLIC NUCLEOTIDES. (Eng.) Strom, T. B. (Peter Bent Brigham Hosp., Boston, Mass.); Hirsch, M. S.; Black, P. H.; Carpenter, C. B.; Phillips, S. M.; Merrill, J. P. *Transplant. Proc.* 7(1/Suppl. 1): 305-307; 1975.

The proliferation of splenic WBC harvested from mice undergoing chronic graft-vs-host (GvH) reaction, as governed by the intracellular levels of the cyclic nucleotides, cyclic AMP and cyclic GMP was studied. The thymidine-methyl- ^3H ($^3\text{H-TdR}$) incorporation in spleens harvested from mice with GMP, was studied. The thymidine-methyl- ^3H ($^3\text{H-TdR}$) by 140% ($p = 0.02$). Chronic GvH disease was produced by the ip injection of BALB/c spleen cells into 6-wk old CAF₁ mice. Carbachol added to cultures at 10^{-11} M resulted in a maximal increase of $144 \pm 6\%$ in $^3\text{H-TdR}$ incorporation. The addition of 8-bromocyclic GMP to GvH spleen cells increased thymidine incorporation by $88 \pm 5\%$ at 10^{-6} M. Dibutyl cyclic AMP, 10^{-3} M and 10^{-4} M, was inhibitory ($82 \pm 8\%$ and $57 \pm 7\%$, respectively). Prostaglandin E₁ (PGE₁) caused a dose-dependent reduction in $^3\text{H-TdR}$ incorporation at 10^{-3} M to 10^{-5} M, with a maximum inhibition of $67 \pm 16\%$ at 10^{-3} M. Theophylline, caused 38% and 22% inhibition of thymidine incorporation at 10^{-3} M and 10^{-4} M, respectively. The combination of PGE₁ (10^{-4} M) and theophylline (10^{-3} M) was additive, inhibiting thymidine incorporation by $78 \pm 8\%$. Cholera toxin (1 $\mu\text{g/ml}$) caused a $69 \pm 7\%$ reduction in $^3\text{H-TdR}$ incorporation. Carbachol and 8-bromocyclic GMP had no effect on normal cells, even when incubations were extended from 1-4 day. Alloimmune-induced WBC proliferation is enhanced by increased cyclic GMP and inhibited by cyclic AMP.

- 6963 LOCALIZATION OF THE β CHAIN OF HUMAN CHORIONIC GONADOTROPIN ON HUMAN TUMOR CELLS AND PLACENTAL CELLS. (Eng.) Naughton, M. A. (4200 E. Ninth Ave., Denver, Colo. 80220); Merrill, D. A.; McManus, L. M.; Fink, L. M.; Berman, E.; White, M. J.; Martinez-Hernandez, A. *Cancer Res.* 35(7):1887-1890; 1975.

Human chorionic gonadotropin (HCG)-like material was identified and localized by peroxidase-labeled antibody to the β chain of HCG in malignant cells of human tumors. Normal rabbit serum controls of all tissues and BeWo cells (from trophoblastic tumor cells of a post gestational human chorioncarcinoma) were consistently negative. In placental tissue control, the syncytiotrophoblast reacted positively with anti- β chain antibody. BeWo cells contained discrete positive cytoplasmic granules. Material reading with anti- β chain antibody was present in the malignant cells of ten human tumors; two breast infiltrating duct carcinomas; one prostatic, one colonic, and one pancreatic adenocarcinoma; one seminoma, one renal cell carcinoma; one liposarcoma; one bronchogenic squamous cell carcinoma; and one transitional cell carcinoma of the kidney. The reaction product of the malignant cells was localized in the cytoplasm with a more intense band of staining at or near the surface. No tumor tissue was unequivocally negative; questionable results were due to the presence of other pigments, extensive necrosis, or intrinsic peroxidase activity. The authors suggest that both selective host immunosuppression by tumors and selective maternal immuno-suppression by fetal tissues may be mediated by HCG.

- 6964 INTERACTION IN CULTURE BETWEEN MOUSE ASCITES HEPATOMA (MH-134) CELLS AND LYMPHOID CELLS OF ISOLOGOUS MICE. (Eng.) Katsuta, H. (Inst. Medical Science, Univ. Tokyo, Shirokanedai, Minato-ku, Tokyo 108, Japan); Ashikawa, K.; Takaoka, T. *Jpn. J. Exp. Med.* 45(4):269-284; 1975.

Mouse mammary carcinoma MM2 cells, known to induce production of humoral antibodies, phagocytosed thymocytes or lymphocytes from mesenteric lymph nodes in a system consisting of tumor cell culture and added thymocytes or lymphocytes. The behavior of mouse ascites hepatoma MH-134, a line regarded to induce production of cellular antibodies, was examined in a similar test system. Cultures of MH-134 cells were set up in roller tubes with flattened surfaces, and the cells were cultured for two weeks before the addition of lymphoid cells. The lymphoid cells were obtained from C3H/He mice bearing s.c.-transplanted MH-134 tumor, and were taken 5, 10, 14, 15, 20, 25, 30, and 40 days after the day of transplantation. Observations of interactions between lymphoid cells and tumor cell cultures were made by analysis of time-lapse cinemicrographs taken immediately and after 1, 2, and 3 weeks. It was found that lymphoid cells were phagocytosed by the MH-134 tumor cells without, in most cases, damage to the tumor cells. However, important exceptions were observed, as follows: When thymocytes from mice bearing MH-134 tumor for 5 days were used, the cultured MH-134 cells

died later. Also, when thymocytes from mice bearing the tumor for 14 or 15 days were used, the cultured MH-134 cells phagocytosed lymphoid cells but died later by burst of cytoplasm. In some cases, the lymphocytes liberated by burst of tumor cells appeared to be alive. The findings suggested the possibility that lymphoid cells attack tumor cells not only from the cell surface but also from the inside after phagocytosis by the tumor cells.

- 6965 HUMAN PROSTATIC TUMORS IN CONDITIONED ANIMALS AND CULTURE. (Eng.) Sato, G. (Dept. Biology, Univ. California at San Diego, La Jolla, Calif. 92037); Desmond, W.; Kelly, F. *Cancer Chemother. Rep. (Part 1)* 59(1):47-49; 1975.

A nude (athymic) mouse colony has been established with a capacity of over 1000 mice. These mice have been injected with human prostatic tumors. A spleen injection method has been developed with makes it possible to follow the growth of tumor cells in the animal for short periods of time and to assess the effects of hormones on this growth. Several animal cell lines in culture and in nude mice have been studied as possible models for a hormone-dependent human prostatic tumor. By using nude mice, it has been shown that apparent "normal" revertants of cancer cells are actually antigenic variants which can be used to immunize animals against the original tumor cells. A melanoma cell line has been developed whose growth appears to be markedly enhanced by androgens. Rat ovarian cell lines have been developed whose growth and viability are hormone dependent *in vivo* and *in vitro*.

- 6966 SOME BIOCHEMICAL STUDIES OF THE METABOLIC INHIBITORY EFFECT OF HUMAN SERUM ON RODENT CELL LINES. (Eng.) Eidinger, D. (Dept. Microbiology, Queen's Univ., Kingston, Ontario, Canada); Mates, A.; Fishler-Mates, Z. *Transplant. Proc.* 7(1/Suppl. 1):537-540; 1975.

Biochemical studies concerning the metabolic inhibitor found in human serum that reduced DNA and RNA synthesis in rodent cell lines are presented. To determine the inhibition kinetics of RNA synthesis in P-815 mastocytoma cells, 0.1 ml of inhibitory human serum and 2 μ Ci of tritiated thymidine were added to 2×10^6 P-815 cells, and then the trichloroacetic acid-insoluble counts/minute were estimated. The addition of human serum significantly suppressed uridine incorporation into RNA; similar data were obtained for the incorporation of tritiated thymidine into DNA as a measure of the DNA inhibition kinetics. The incorporation of tritiated uridine into the acid-insoluble fraction paralleled the total counts when determined on cell cultures over periods of time from 15 min to two hours, indicating that the free pool of intracellular uridine was the same in all cultures tested at any one time whether the serum was present or not. To determine the effect of human serum in the synthesis of vesicular stomatitis virus (VSV) in mouse L-cell monolayer cultures, 0.1

ml of undiluted human serum was mixed with VSV and added to the mouse L-cells. The degree of the virus inhibition correlated well with the degree of inhibition of RNA synthesis in P-815 cells. However, as measured by the plaque assay in culture to which heat-inactivated serum was added, the virus synthesis did not completely disappear in comparison to the total disappearance of the inhibition of uridine incorporation into RNA of the P-815 cells. The results indicate a fundamental defect in the biochemical synthetic mechanisms in inhibited cells. The equivalent differences throughout the culture period suggest that cell transport is unaffected, but rather that inhibition occurs at the synthesis of nucleic acids.

- 6967 *IN VITRO* PROLIFERATIVE RESPONSE OF BALB/c MOUSE SPLEEN CELLS STIMULATED WITH TRINITROPHENYLATED SYNGENEIC SPLEEN CELLS. (Eng.) Tokuyama, H. (Cancer Res. Inst., Kanazawa Univ., 13-1, Takaramachi, Kanazawa, Japan). *Immunology* 29(5):875-884; 1975.

A study was conducted to determine if normal spleen cells can react to hapten-conjugated syngeneic spleen cells in mixed lymphocyte culture. Trinitrophenylated (TNP) spleen cells were prepared by treating normal BALB/c mouse spleen cells with sodium 2,4,6-trinitrobenzenesulphonate (TNBS, 2-5mM, 30 min, 25°C). Four-day cultures of TNP-labeled spleen cells incorporated 2.5-7.4 times more [³H]thymidine than did similar cultures of untreated spleen cells. An obviously positive mixed lymphocyte reaction (MLR) by normal spleen cells against mitomycin C (MC)-treated TNP-labeled syngeneic spleen cells was observed after four days of culture. The MLR to TNP-labeled syngeneic cells was inhibited in the presence of ϵ -trinitrophenyl-L-lysine (10^{-5}) by 23-37%. The spleen cells from the mice injected ip with TNP-labeled syngeneic spleen cells showed a higher MLR against TNP-labeled spleen cells than normal spleen cells. The sensitized spleen cells also showed an increased response to MC-treated spleen cells. These results suggest that normal spleen cells include cells that can recognize the hapten and new antigenic determinants introduced into syngeneic spleen cells by chemical modification.

- 6968 ADENOSINE INHIBITION OF LYMPHOCYTE MEDIATED CYTOLYSIS: POSSIBLE ROLE OF CYCLIC ADENOSINE MONOPHOSPHATE. (Eng.) Wolberg, G. (Wellcome Res. Lab., Res. Triangle Park, N.C.); Zimmerman, T. P.; Hiemstra, K.; Winston, M.; Chu, L. C. *Science* 187(4180):957-959; 1975.

- 6969 CELL-MEDIATED IMMUNITY TO ANTIGENS ASSOCIATED WITH ENDOGENOUS MURINE C-TYPE LEUKEMIA VIRUSES. (Eng.) Hirsch, M. E. (Massachusetts Gen. Hosp., Boston); Kelly, A. P.; Proffitt, M. R.; Black, P. H. *Science* 187(4180):959-961; 1975.

- 6970 J CHAIN IN MALIGNANT HUMAN IgG IMMUNOCYTES. (Eng.) Brandtzaeg, P. (Dental Faculty, Univ. of Oslo, Blindern, Oslo, Norway); Berdal, P. *Scand. J. Immunol.* 4(4):403-407; 1975.

- 6971 LYMPHOCYTE CYTOTOXICITY TO LEUKEMIC BLAST CELLS BY NORMAL INDIVIDUALS [abstract]. (Eng.) Klein, D. L. (Johns Hopkins Univ. Oncol. Cent., Baltimore, Md.); Anderson, P. N.; Santos, G. W. *Proc. Am. Assoc. Cancer Res.* 16:149; 1975.

- 6972 KINETICS OF HUMAN LYMPHOCYTE PROLIFERATION: PROPORTION OF CELLS RESPONSIVE TO PHYTOHEMAGGLUTININ AND CORRELATION WITH E ROSETTE FORMATION. (Eng.) Nowell, P. C. (Sch. Med., Univ. Pennsylvania, Philadelphia); Daniele, R. P.; Winger, L. A. *J. Reticuloendothel. Soc.* 17(1):47-56; 1975.

- 6973 NEONATAL PRESENCE OF T-CELL SUBPOPULATION IN SPLEEN OF AKR MICE [abstract]. (Eng.) Fernandes, G. (Univ. Minnesota Hosp., Minneapolis); Yunis, E. J. *Am. J. Pathol.* 78(1):26a; 1975.

- 6974 HUMAN LYMPHOCYTES: 5'-NUCLEOTIDASE-POSITIVE AND -NEGATIVE SUBPOPULATIONS. (Eng.) Silber, R. (New York Univ. Sch. Medicine, New York, N.Y. 10016); Conklyn, M.; Grusky, G.; Zucker-Franklin, D. *J. Clin. Invest.* 56(5):1324-1327; 1975.

- 6975 CYTOCHEMICAL CHARACTERISTICS OF LYMPHOCYTES OF THE PERIPHERAL BLOOD AND LYMPH NODES IN LYMPHOGRANULOMATOSIS IN CHILDREN. (Rus.) Zharov, V. N. (Inst. Pediatrics, Acad. Medical Sciences of the USSR, Moscow, USSR). *Pediatrics* (8):23-26; 1975.

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- 6978 REAPPEARANCE OF NEONATAL SENSITIVITY TO AN ONCOGENIC VIRUS IN SENESCENT MICE AS A SPECIFIC CONSEQUENCE OF IMMUNOLOGIC DECAY [abstract]. (Eng.) Pazmino, L. (Univ. Tennessee); Nelson, H. *Diss. Abstr. Int. B.* 35(11):5252-5253; 1975.

- 6979 REQUIREMENTS FOR DIVALENT CATIONS BY HORMONAL MITOGENS AND THEIR INTERACTIONS WITH SEX STEROIDS. (Eng.) Morgan, J. I. (Dept. Biologi-

- cal Sciences, Univ. Aston in Birmingham, Gosta Green, Birmingham B4 7ET, England); Hall, A. K.; Perris, A. D. *Biochem. Biophys. Res. Commun.* 66(1):188-194; 1975.
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- 6982 PROTECTIVE TUMOUR CELL GHOSTS WITH INTACT MEMBRANE MARKERS. (Eng.) Davies, I. ab I. (Sub-dept. Immunology, Liverpool Univ., Liverpool L69 3BX, UK); Nicklin, M. G.; Augustin, R. *Nature* 256(5512):49-50; 1975.
- 6983 DETECTION OF CELL-DEPENDENT ANTIBODY TO MONOLAYER CULTURE TARGET CELLS DERIVED FROM NORMAL AND NEOPLASTIC TISSUES [abstract]. (Eng.) Kodera, Y. (Mem. Sloan-Kettering Cancer Cent., New York, N.Y.); Bean, M. A. *Proc. Am. Assoc. Cancer Res.* 16:194; 1975.
- 6984 TRANSIENT IMPAIRED CELL-MEDIATED TUMOR IMMUNITY AFTER ACUTE INFECTION WITH LYMPHOCYTIC CHORIOMENINGITIS VIRUS. (Eng.) Guttler, F. (Inst. Medical Microbiology, 22 Juliane Maries Vej, DK-2100, Copenhagen, Denmark); Bro-Jørgensen, K.; Jørgensen, P. N. *Scand. J. Immunol.* 4(4):327-336; 1975.
- 6985 TUMOR IMMUNITY IN MARMOSETS TO ONCORNAVIRUS-TRANSFORMED CELL LINES [abstract]. (Eng.) Massey, R. J. (Rush-Presbyt.-St. Luke's Med. Cent., Chicago, Ill.); Johnson, T. R. *Proc. Am. Assoc. Cancer Res.* 16:113; 1975.
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- 6997 SOLUBILIZATION AND CHARACTERIZATION OF MOUSE P-815 MASTOCYTOMA MEMBRANE ANTIGENS [abstract]. (Eng.) Clemetson, K. J. (Theodor-Kocher-Inst., CH-3000 Bern 9, Switzerland); Bertschmann, M.; Luscher, E. F. *Experientia* 31(6):718; 1975.
- 6998 EXTRACTION OF TUMOR ANTIGENS FROM A HUMAN MELANOMA CELL STRAIN GROWN IN CHEMICALLY DEFINED MEDIUM [abstract]. (Eng.) Chee, D. O. (Sepulveda Veterans Adm. Hosp., Calif.); Morton, D. L.; Holmes, E. C. *Proc. Am. Assoc. Cancer Res.* 16:168; 1975.
- 6999 PURIFICATION OF HUMAN MELANOMA-ASSOCIATED ANTIGEN [abstract]. (Eng.) Roth, J. A. (Sepulveda Veterans Adm. Hosp., Calif.); Holmes, E. C.; Reisfeld, R. A.; Morton, D. L.; Eilber, F. R. *Proc. Am. Assoc. Cancer Res.* 16:146; 1975.
- 7000 STUDY OF ANTIGENS ASSOCIATED WITH HUMAN BREAST CARCINOMA. (Rus.) Kriukova, I. N. (N. F. Gamaleya Inst. Epidemiol. Microbiol., U.S.S.R.); Vasilevskaya, L. N. *Vopr. Onkol.* 21(2):52-56; 1975.
- 7001 A COMMON ANTIGEN UNIQUE TO CULTURED CERVIX SQUAMOUS CARCINOMA (CSC) DEMONSTRATED WITH XENOGENEIC ANTISERA [abstract]. (Eng.) Herschman, H. R. (Univ. California Los Angeles Med. Cent.); Rose, S. P.; Byfield, J. E.; Passovoy, D. *Proc. Am. Assoc. Cancer Res.* 16:110; 1975.
- 7002 SARCOMA ASSOCIATED TUMOR ANTIGEN EXPRESSION IN DIFFERENT PHASES OF THE CELL CYCLE [abstract]. (Eng.) Burk, K. (M. D. Anderson Hosp. and Tumor Inst., Houston, Tex.); Drewinko, B.; Lichtiger, B.; Trujillo, J. M. *Proc. Am. Assoc. Cancer Res.* 16:178; 1975.
- 7003 QUANTITATION OF ANTIGENS IN NORMAL AND MALIGNANT OVARIAN TISSUE. (Eng.) Knauf, S. (Wellesley Hosp., 160 Wellesley St. E., Toronto, Ontario, Canada); Urbach*, G. I. *Am. J. Obstet. Gynecol.* 123(3):302-304; 1975.
- 7004 IMMUNITY TO HUMAN TUMOR-ASSOCIATED ANTIGENS MEDIATED BY "IMMUNE" RNA [abstract]. (Eng.) Kern, D. H. (Harbor Gen. Hosp., Torrance, Calif.); Pilch, Y. H. *Proc. Am. Assoc. Cancer Res.* 16:152; 1975.
- 7005 CELL-MEDIATED IMMUNE RECOGNITION OF TUMOR ASSOCIATED ANTIGENS (TAA) IN A SV 40 VIRUS-INDUCED TUMOR OF BALB/c MICE [abstract]. (Eng.) Dean, J. H. (Litton Bionetics, Inc., Kensington, Md.); McCoy, J. L.; Maurer, B. A.; Lewis, D. D.; Howell, S. B.; Appella, E.; Law, L. W. *Proc. Am. Assoc. Cancer Res.* 16:149; 1975.
- 7006 IMMUNOLOGIC DISSIMILARITY BETWEEN HUMAN TUMOR-ASSOCIATED ANTIGEN(S) AND HETEROLOGOUS ANTIGENS [abstract]. (Eng.) Gupta, R. K. (Univ. California Los Angeles Med. Sch.); Yee, R.; Irie, R. F.; Morton, D. L. *Proc. Am. Assoc. Cancer Res.* 16:147; 1975.
- See also:
- * (Rev): 6615, 6621, 6625, 6626, 6627, 6628, 6629, 6630, 6658, 6659, 6660, 6661, 6665, 6666, 6667, 6668, 6669
 - * (Chem): 6708
 - * (Phys): 6817
 - * (Viral): 6831, 6841, 6848, 6868, 6881, 6885, 6904
 - * (Path): 7050, 7052, 7053, 7057, 7058, 7059, 7064, 7097
 - * (Epid-Biom): 7136, 7144

- 7007 THE POSSIBILITY OF LATENT CENTROMERES AND A PROPOSED NOMENCLATURE SYSTEM FOR TOTAL CHROMOSOME AND WHOLE ARM TRANSLOCATIONS. (Eng.) Hsu, T. C. (Univ. Texas M.D. Anderson Hosp. and Tumor Inst., Houston, Tex. 77025); Pathak, S.; Chen, T. R. *Cytogenet. Cell Genet.* 15(1):41-49; 1975.

The possible existence of latent centromeres is discussed, and a nomenclature system for identifying the origin and nature of the chromosomal rearrangements is proposed. Karyotype analyses of various human cancer cells have revealed compound chromosomes involving total chromosomes and chromosome arms. Banding shows no substantial chromatin loss. Two possible explanations for this are offered: centromeric deletion and centromeric inactivation. The occasional dicentric chromosome morphology found in a case of (X;X) translocation supports the concept of centromere inactivation. Translocations involving total chromosomes or whole chromosome arms are classified into three basic types. Centromere-centromere (Robertsonian) translocations, most frequently showing constitutive heterochromatin in the centromeric areas, could possibly be dicentric. Centromere-telomere (C-T) translocations, as identified by Q- and G-banding, need not require the loss of a centromere. The tandem translocations and telomeric fusions of telomere-telomere (T-T) translocations suggest a role of chromosome "fission" in karyologic evolution. C-T and T-T translocations also support the concept of the existence of interstitial telomeres, as suggested by the repeated discovery of interstitial C-bands. Thus the presence and reactivation of such latent centromeres could explain the acquisition of additional functional centromeres in chromosomal fission or fragmentation. A nomenclature system proposes the use of the symbol "K" for the functional centromere, "(k)" for deleted centromere, and "k" for a centromere of uncertain nature.

- 7008 CHROMOSOME CHANGES IN THE BLASTIC TRANSFORMATION STAGE OF CHRONIC GRANULOCYTIC LEUKAEMIA. (Eng.) Garson, O. M. (St. Vincent's Hosp., Melbourne, Australia); de Gruchy, G. C. *Haematologia* 8(1/4):21-27; 1975.

The incidence and nature of chromosome abnormalities (in addition to the Philadelphia chromosome [Ph¹]) together with the changes occurring following combination anti-leukemic treatment were investigated in patients in the blastic transformation stage of chronic granulocytic leukemia. Karyotyping was performed by Giemsa banding. Ph¹ was present in the bone marrow cells of all patients. Of the 30 patients (19 males, 11 females), 28 yielded satisfactory chromosome preparations. All 28 patients had chromosome abnormalities: 19 hyperploidy, seven hypoploidy, and two pseudoploidy. In cells with hyperploidy, usually 47-53 chromosomes were present and the most common additional chromosome was usually of the C group. In all cases, hypoploidy referred to 45 chromosomes/cell and the missing

chromosome was most often of the C group. Chemical and hematological remission occurred in 11 patients following therapy (by 3-22 months); all reverted to a 46 Ph¹ positive line. Blastic transformation of Ph¹ positive chronic granulocytic leukemia was accompanied by additional chromosome abnormalities in all but two of 30 cases, indicating that the presence of the Ph¹ chromosome predisposes the leukemic cell to further chromosome aberration. The appearance of additional abnormalities is a reliable indication of transformation. Thus, the Ph¹ chromosome has a major role in the pathogenesis of chronic granulocytic leukemia. The incidence of chromosome abnormalities found in this study is higher than that in acute leukemia, further supporting this view.

- 7009 AUTORADIOGRAPHIC AND FLUORESCENT STAINING STUDIES OF BONE MARROW CHROMOSOMES FROM A PATIENT WITH ACUTE GRANULOCYTIC LEUKEMIA. (Eng.) Sofuni, T. (Japan Natl. Inst. Health, Hiroshima Branch Clin. Lab., Japan); Okada, H. *Cancer* 35(2):378-384; 1975.

The chromosome constitution and cytogenetic features of a seven-yr-old patient with acute granulocytic leukemia were characterized using autoradiographic and fluorescent staining techniques. In two samples of bone marrow, the cells had a modal chromosome number of 43. Abnormal karyotypic patterns observed on detailed analysis did not appear to be random loss or gain of certain chromosomes, but seemed to be related to certain specific groups of chromosomes. The following abnormalities were seen in these cells: three chromosomes were missing, one each from groups B4-5, C6-X-12, and an E17. This abnormal constitution was found in 17 (65%) of 26 cells with a modal number of 43. An additional element in group G21-22 was more frequent in the second sample. The characteristic fluorescent pattern of chromosomes in most leukemic cells from a 24-hr marrow culture was indistinct, and the presumed Y chromosome did not show a bright fluorescing pattern. Labeling frequency of bone marrow leukemic cells in 24-hr cultures was lower than that of normal marrow cells in 72-hr cultures. The labeling frequency of the leukemic cells was lower during short (6 hr) culture than during 24 hr culture. The authors suggest that these findings indicate that the duration of G₂ period of leukemic cells is longer than that of normal cells *in vitro*, but may shorten with prolonged culture time.

- 7010 HEMATOLOGICAL AND GENETIC STUDY OF A NEONATAL ACUTE MYELOBLASTIC LEUKEMIA. (Eng.) Larripa, I. (Instituto Investigaciones Hematológicas, J. A. Pacheco de Melo 3081, Buenos Aires, Argentinian); Brieux de Salum, S.; Pavlovsky, S. *Sangre (Bare.)* 20(1):69-73; 1975.

A case of acute myeloblastic leukemia diagnosed in a 5-day-old male is presented. On the second day of life, the infant developed diarrhea, hepatosplenomegaly, and pallor. Blood study on the fifth day led to the diagnosis of acute myeloblastic

leukemia (100% undifferentiated blasts in the bone marrow of the tibia). Treatment was begun with vincristine and prednisone, complete remission with bone marrow showing less than 5% blasts was obtained after four weekly injections of vincristine. The child was asymptomatic and gained 1.5 kg by 9 weeks of age, when splenomegaly recurred with 4% blasts in a peripheral blood smear. Despite renewed treatment with vincristine and prednisone, death occurred at 26 weeks from cerebral hemorrhage. Dermatoglyphic studies showed a complete absence of Edward's syndrome and mongolism. The authors suggest that the aberrations of chromosomes 17 and 18 may have been caused by the same process that gave rise to the leukemia. These alterations were not attributable to any genetic syndrome.

- 7011 ULTRASTRUCTURE OF THE BONE MARROW CELLS IN THE PATIENTS WITH ACUTE ERYTHROMYELOSIS AND ACUTE ERYTHROLEUKEMIA. (Rus.) Demin, A. A. (Faculty Hosp. Ther., Novosibirsk Medical Ins., USSR); Degtyareva, M. M.; Vakulin, G. M. *Probl. Gematol. Pereliv. Krovi* 20(3):13-17; 1975.

An electron microscopic study of the bone marrow cells from nine patients (four men and five women, aged 24 to 69 yr) with erythromyelosis and erythroleukemia revealed ultrastructural changes and developmental asynchronism of the nuclei and cytoplasm in erythroid, granulocytic, and megakaryocytic elements. Particularly marked disturbances were observed in the submicroscopic structure and metabolism in cells of the erythroid series: changes in nuclear and cytoplasmic shape, multinuclearity, a prevalence of monoribosomes in the early stages of maturation, altered mitochondria, the presence of an iron-containing substance in the mitochondria and cytoplasm, and the presence of glycogen, lipids, and vacuoles in the cytoplasm. These changes were evidence of intramedullary hemolysis and acquired sideroachrestic anemia. Asynchronism in nuclear and cytoplasmic development in granulocytic elements was evidence of their morphological immaturity, while megakaryocytes, in addition to this developmental asynchronism, showed an insufficient quantity of glycogen in the cytoplasm. Evidently all hemopoietic elements are involved in the pathological process in cases of acute erythromyelosis and acute erythroleukemia.

- 7012 CHRONIC MYELOID LEUKEMIA. (Fre.) Waitz, R. (Centre departemental de Transfusion sanguine, 10, rue Speilmann, 67000 Strasbourg, France); Mayer, S.; Mayer, G.; Oberling, F. *Nouv. Rev. Fr. Hematol.* 15(2):213-228; 1975.

Myelosclerosis during chronic myeloid leukemia (CML) and the relation between this disease and acute transformation were studied in 64 cases. Differential diagnosis of CML and primary myelosclerosis or myeloid splenomegaly was based on the number of leukocytes and the percentage of early myeloid forms before treatment, the presence of Philadelphia chromosomes in the blood or bone marrow, leukocytic

alkaline phosphatase, the changes in erythroblast and RBC counts, and on studies of intravascular hematopoiesis (frequent in primary myelosclerosis and rare in secondary forms). Myelosclerosis was observed in two forms at the first examination: a generalized or systematized form, 48% or a fractionated form, 19%. Previous treatment and the length of development before the first examination had no effect on the disease. At the first examination, 47 patients had received no previous treatment; myelosclerosis was found among 70% of these and the average length of evolution of the disease was three months, 13 days. Subsequent examinations revealed an increase in myelosclerosis as well as an increase in intensity. In 17 cases, trepanopuncture was effected three or more times; the last examination revealed 13 cases of generalized myelosclerosis (nine intense myeloscleroses), three fractionated cases, and one absence of myelosclerosis. A femoral sample, taken shortly after death was compared to a trepanopuncture. Among these 17 patients, 15 were found to have acute transformation with sclerosis, one had pure sclerosis. In most cases, the lesions were comparable in terms of type and degree of myelosclerosis and osteosclerosis. In five cases, however, large patches of pure sclerosis were found in the femoral marrow. At first examination, a generally moderate acute transformation was associated with myelosclerosis in 24 cases and was present alone in 10; sclerosis appeared alone in 19 cases and both acute transformation and sclerosis were absent in 11. The degree of myelosclerosis and acute transformation rose in parallel. The results demonstrate, in contrast to previous studies, that the appearance of myelosclerosis and acute transformation in part of the natural development of CML.

- 7013 HODGKIN'S DISEASE DEVELOPING IN ACUTE LEUKEMIA. REPORT OF TWO CASES. (Fre.) Armenta, D. (Departement de Medecine, Hotel-Dieu de Montreal, Montreal, Canada); Pretty, H. M.; Long, L. A.; Neemeh, J. A.; Gosselin, G. *Union Med. Can.* 104(5):744-748; 1975.

Two cases of acute leukemia occurring with Hodgkins disease are described to clarify the role of radiotherapy and chemotherapy in the etiology of the leukemia. Hodgkins disease of the sclerosing nodular type was diagnosed in a female patient, age 39, in 1967. After treatment with 3,300 rads to the mediastinal and cervico-clavicular region, the patient remained asymptomatic until 1970. Additional radiotherapy, 3,000 rads, was administered to the axillary region. In September, 1971, the disease invaded the liver and abdomen and chemotherapy with Mustargen, Oncovin, Procarbazine, and Prednisone (M.O.P.P.) was begun. Pancytopenia first appeared in June, 1973 and the patient was taken off the M.O.P.P. regimen and bleomycin (30 mg/wk iv for 10 wk) was administered. The blood picture at this point was that of hypochromic anemia with leukemic-like reaction. Not until February, 1974 was the blood picture confirmed as that of acute myeloid leukemia. Death occurred in 1974 and autopsy revealed leukemic infiltra-

tion of all organs, particularly the liver, cardiac muscle and brain, without evidence of Hodgkins disease. The second case was a 54-yr-old male with paraganulomous Hodgkins disease treated with 40 mg iv Mustargen in 1969 and chronic dosage with Leukeran, 2 mg tid, until December 1970 when the dosage was reduced. Pancytopenia appeared in May, 1971 during a course of radiotherapy for retroperitoneal lymph node involvement. Total dose of radiotherapy was 3,600 rads below the diaphragm and 1,800 rads in the mediastinal region. Bleomycin treatment was instituted for the pancytopenia in September, 1973. Acute leukemia of myeloblastic type was diagnosed in January, 1974 and the patient died in September, 1974. Autopsy revealed leukemic infiltration and widespread Hodgkins disease. Suppression of the immunological system by the chemotherapy and radiotherapy is proposed as a mechanism in development of the neoplastic process.

- 7014 MICROORGANISM-LIKE STRUCTURES IN HODGKIN DISEASE: ELECTRON MICROSCOPICAL DEMONSTRATION. (Eng.) Parmley, R. T. (Med. Univ. South Carolina, Charleston); Spicer, S. S.; Pratt-Thomas, H. R.; Morgan, S. K.; Othersen, H. B. *Arch. Pathol.* 99(5):259-266; 1975.

The observation of a structure resembling mycoplasma in lymph nodes from patients with untreated mixed cell Hodgkin disease is reported. Lymph nodes were removed surgically and thin sections were stained with uranyl acetate and lead citrate and examined with the electron microscope. Of the 12 cases of Hodgkin disease thus examined, nine were of the mixed cell variety, as demonstrated by numerous eosinophils, conspicuous clusters, trabeculae, and even sheets of reactive histiocytes, plus classical binucleated Reed-Sternberg cells. In addition to the common ultrastructural features of the large Hodgkin cells and Reed-Sternberg cells, small membrane-limited structures of 200-500 mμ in diameter were observed in the lymph nodes of 50% of the patients with mixed cell disease. The structures were spherical, of a matrix more dense than the surrounding cytoplasm, and they contained 20-50 closely packed electron-opaque ribosome-like particles 100-200 Å in diameter. The spheroids were found in the extracellular space and in disrupted cells, and within reticular cells, macrophages, mononuclear cells, and, occasionally, in tumor cells. In the extracellular space, they occurred singly or in groups in close proximity to reticular cells; however, intracellularly, they occurred individually or in groups within otherwise lucent, membrane-limited vacuoles. The distinct morphologic characteristics and distribution of the spheroids indicated the possibility of being microorganisms; the numerous pleomorphic forms resembled the demonstrated developmental stages of mycoplasma. Spheroids were found in half of the patients with mixed cell Hodgkin disease, even in tumor-free lymph nodes. Their occurrence may be a manifestation of an impaired immune response to infectious agents, or the representation of mycoplasma elementary bodies.

- 7015 PROPOSITION FOR A CLASSIFICATION OF THE NON-HODGKINIAN LYMPHOSARCOMAS. (Fre.) Diebold, J. (Hôtel-Dieu, 1, Place du Parvis Notre-Dame, 75181 Paris Cedex 04, France). *Ann. Anat. Pathol. (Paris)* 20(1):35-42; 1975.

A new morphological classification of non-Hodgkins lymphosarcomas is proposed based on recent data on the origin and evolution of lymphocytes. Classification utilizes routine staining techniques: hematoxylin-eosin-safranin, Giemsa, and PAS. Tumors of lymphoid tissue are classified as monomorphic (composed of single lymphocyte cell type) or pleomorphic (composed of more than one type lymphatic tissue cell). There are four cell types derived from lymphatic tissue: the small lymphocyte, lymphoblast, immunoblast, and plasmocyte. Tumors composed principally of lymphocytes are categorized as lymphosarcomas, monomorphic or pleomorphic. Immunoblastosarcomas are tumors composed of immunoblasts with either regular nuclei (i.e., Burkitt's lymphoma), or irregular nuclei, or the plasmocytic immunoblastosarcoma which resembles the other two types but has a distinctive pattern of immunoglobulin production. The plasmocytic sarcoma (e.g., a rare type of non-bony tissue multiple myeloma) is composed principally of proplasmocytes, plasmocytes, and some plasmoblastic type cells. Two other categories-histocytic sarcomas and non-classified sarcomas are included because of lack of more accurate classification information. Sarcomas can be further categorized as nodular or diffuse. The nodular sarcomas are less malignant than the diffuse sarcomas of a similar cell type. The author suggests that this morphological categorization of non-Hodgkins lymphoid tissue sarcomas can be readily translated into a functional categorization when experimental research has clearly defined the roles of the T and B lymphocytes.

- 7016 FANCONI SYNDROME IN ADULTS: A MANIFESTATION OF A LATENT FORM OF MYELOMA. (Eng.) Maldonado, J. E. (Mayo Clin., Rochester, Minn.); Velosa, J. A.; Kyle, R. A.; Wagoner, R. D.; Holley, K. E.; Salassa, R. M. *Am. J. Med.* 58(3):354-364; 1975.

From a review of 17 cases of Fanconi syndrome with Bence Jones proteinuria and myeloma or amyloidosis including three new case studies, there emerges a well-defined set of characteristics. In case one, a 60-yr-old Caucasian male, estimated at having had Fanconi syndrome for 16.5 yr, had no diagnosis of myeloma, but experienced systemic amyloidosis shortly before his death; autopsy revealed involvement of the tongue, heart, colon, and bone marrow. Lymphoplasmacytic elements of the bone marrow contained cytoplasmic inclusions. The metabolic bone disease responded symptomatically to pharmacologic doses of vitamin D. In case two, a 67-yr-old Caucasian female had proteinuria and glycosuria for 14 and 13 yr, resp., and had documented Fanconi syndrome five yr prior to her death as a result of myeloma. Diagnosis of myeloma was not confirmed until autopsy,

with cytoplasmic inclusion bodies present. Case three involved a 50-yr-old Caucasian male of diagnosed Fanconi syndrome (five yr), proteinuria (nine yr), but no diagnosis of myeloma; throughout the study, this patient remained asymptomatic. Electron microscopic studies of lymphoplasmacytic elements of aspirated bone marrow revealed the presence of cytoplasmic inclusion bodies of increased but variable electron density. These inclusion bodies reportedly appeared most often as needle- or rod-shaped structures, homogenous or with a linear periodicity of 85-105 Å, and were invariably surrounded by agranular or smooth membranes. Well-defined electron dense inclusion bodies were also seen in the cytoplasm of kidney tubular cells. Indications of Fanconi syndrome preceded the diagnosis of myeloma or amyloidosis in 11 of 17 patients, with the premyeloma phase lasting as long as 16.5 yr; no cases were reported where myeloma preceded the development of Fanconi syndrome. Multiple myeloma was found to cause non-specific demineralization alone in two patients, but was frequently accompanied by characteristic osteolytic lesions. All but one patient had plasmacytic dyscrasia at some point in his disease. Cytoplasmic inclusion bodies were found in the lymphoplasmacytic elements; these were surrounded by smooth membranes and displayed morphological similarity to those found in marrow plasma cells and renal tubular cells. All patients typed thus far had the kappa type of Bence Jones protein.

- 7017 LIVER DISEASE AMONG POLYVINYL CHLORIDE PRODUCTION WORKERS. (Eng.) Creech, J. L., Jr. (Dep. Surg., Univ. Louisville, Ky.); Makk, L. *Ann. N.Y. Acad. Sci.* 246:88-94; 1975.

A protocol for systematic testing of all employees of a chemical plant producing polyvinyl chloride (PVC), ABS resins, and specialty synthetic rubber is presented. An attempt to relate liver abnormality to the degree of vinyl chloride exposure resulted in the determination of five categories of work areas; the highest exposure was in the area of PVC production, followed sequentially by other areas of production, PVC maintenance personnel, other maintenance employees, and all other employees. A standard sequential multiple analysis (SMA-12) was the initial test used, repeated at a maximum of every six mo. On the presentation of elevated liver function tests, the consequent special procedures included fractionation of lactate dehydrogenase (LDH), determination of alkaline phosphatase activity, total bilirubin, complete blood count, chest x-rays, a liver spleen scan, plus liver biopsies when indicated. On original examination of 1183 employees, 26.6% had one abnormal test, 3.5% had two or more abnormal tests; abnormalities persisted in 24% of those retested. The battery of tests on 116 employees indicated major or persistent abnormalities in 17 of them. Two of these had angiosarcoma. While a correlation of abnormal SMA-12 examinations with the various areas of production was obscure, 10% of the workers in PVC production exhibited abnormal tests, as compared to 4.1% abnormal for other areas of production. Whereas the alkaline phosphatase level was the

most frequently elevated, there was no single outstandingly abnormal test. Results of 17 liver biopsies revealed two angiosarcomas and five normal reports; periportal fibrosis was otherwise found most common. Fractionation of LDH showed isolated factor four elevations in 66% of the employees. A very high incidence of creatine phosphokinase was found in 75% of the Negro workers, as compared to 12% of the Caucasians. It was concluded that no one isolated test provided an adequate evaluation, that the special procedures appeared quite accurate, and that such studies should be continued through the years and beyond retirement.

- 7018 IDENTIFICATION OF PREMALIGNANT HYPERPLASIA IN METHYLCHOLANTHRENE-INDUCED MAMMARY TUMORIGENESIS. (Eng.) Fisher, E. R. (Shadyside Hosp., Pittsburgh, Pa. 15232); Shoemaker, R. H.; Palekar, A. S. *Lab. Invest.* 33(4):446-450; 1975.

Cytogenic studies and methylcholanthrene (MCA) treatment of a hormone-induced hyperplasia, were evaluated in determining its significance and relationship to breast cancer. Fifty-day-old Wistar-Furth rats underwent splenectomy. Thirty rats were injected sc with 4 mg progesterone three times weekly, for eight weeks. Thirty rats received an injection of 15 µg β-estradiol, and two additional groups received estradiol or progesterone plus intragastric instillation of 20 mg MCA. Tissues were cultured and aliquots were fixed for light microscopy or transplanted sc into the flanks of matched recipients. No nodules were detected in rats receiving only hormones, while those receiving MCA plus estradiol or progesterone developed palpable mammary nodules and occasional pulmonary metastases (25% and 15% of rats treated with MCA and estradiol or progesterone, respectively). Animals of all groups developed mammary hyperplasia, which were initially histologically indistinguishable. The hyperplastic changes were characterized by tubular adenocystic and papillary arrangements; only those designated as cancer showed a desmoplastic stroma. Only cells from the lesions of rats receiving the hormones and MCA exhibited significant chromosomal aberrations. These included aneuploidy and major aberrations in 10% of the cells. Qualitatively similar chromosomal changes were noted in 25% and 40% of the cells in lesions regarded as advanced hyperplasia and cancer, respectively; chromosome numbers ranged from 38-178 and 40-166 respectively. Thus, quantitative but not qualitative chromosomal differences distinguished these lesions; chromosome analysis represents a useful technique for this discrimination.

- 7019 DILEMMA IN A CASE OF TURCOT'S (GLIOMA-POLYPOSIS) SYNDROME: REPORT OF A CASE. (Eng.) Rothman, D. (135 Maple Ave., Red Bank, N.J. 07701); Su, C. P.; Kendall, A. B. *Dis. Colon Rectum* 18(6):514-515; 1975.

Five previously documented cases of the Turcot (or glioma-polyposis) syndrome are reviewed, and a new case is presented. The first five cases can be

summarized as follows: (a) a 24-yr-old man who died from a medulloblastoma and had previously suffered from a rectal polyp showing adenocarcinoma; (b) a 15-yr-old boy with adenocarcinoma and carcinoma in a rectal polyp who died two years later of medulloblastoma; (c) the 13-yr-old sister of the previous patient who manifested benign polyposis and died at age 21 from left frontal glioblastoma; (d) an 80-yr-old man who had frontal glioblastoma and polyposis coli; and (e) a family in which four members with various types of colonic or rectal polyposis subsequently died of temporal lobe glioma, thalamic glioblastoma, frontal glioblastoma, or fronto-parietal glioblastoma. The sixth case is a 28-yr-old man who had resection of a right cerebellar medulloblastoma and whole brain radiotherapy. Sigmoidoscopy showed polyps, and a barium-enema study confirmed total colonic polyposis; random biopsy showed them to be benign. Sigmoidoscopy and barium-enema examination are warranted in suspected glioma patients, and, in reverse, polyposis patients and their families should be observed for neurologic change.

7020 THE ULTRASTRUCTURE OF N-DIBUTYLNITROSAMINE INDUCED PULMONARY TUMOURS (ADENOCARCINOMATA) IN EUROPEAN HAMSTERS. (Eng.) Reznik-Schuller, H. (Abteilung für Experimentelle Pathologie Medizinische Hochschule Hannover, 3000 Hannover-Kleefeld, Karl-Wiechert-Allee 9, West Germany); Mohr, U. *Br. J. Cancer* 32(2):230-238; 1975.

N-Dibutyl nitrosamine-induced pulmonary adenocarcinomas in European hamsters were examined by electron microscope in an attempt to determine the histogenesis of these tumors. Two male and two female hamsters were treated *sc* once a week for life with 61.1 and 46.7 mg/kg N-dibutyl nitrosamine, respectively. Moribund animals were anesthetized and with the thorax closed were perfused *via* the portal vein with Rheomakrodex and fixed *in situ* by perfusion with 2% cacodylate buffered glutaraldehyde. To milliliters of the fixative were then instilled intratracheally. Tissue samples from macroscopically visible lung tumors were fixed in osmium tetroxide, dehydrated in ethanol and embedded in Epon. Semi-thin sections were stained with toluidine blue, and ultrathin sections were stained with uranyl acetate and lead citrate. All four animals developed lung tumors, and two also developed neoplasms of the urinary bladder (two transitional cell carcinomas and one transitional cell papilloma). Semi-thin sections revealed the pulmonary neoplasms to be composed of densely packed light and dark cells. In two cases they were closely associated with smaller bronchi, the basement membranes of which appeared penetrated. Electron microscopy revealed both light and dark tumor cells to have a similar ultrastructure, the differences in their density being caused by less densely packed cytoplasmic organelles. The most characteristic feature of both light and dark cells was the presence of lamellar bodies closely resembling those occurring in alveolar epithelial cells Type II of normal lung tissue. Two main structural forms were distinguished: the more frequently occurring type contained cross-

barred lamellae and the second type had concentrically arranged lamellae. Both types often contained various amounts of an electron dense, finely granulated lysosome-like material from which the lamellae seemed to originate. In the bronchi, seen to be continuous with the tumor tissue, at points distant from the defect in the basement membrane, cells containing lamellar bodies closely resembling those found in the tumor cells were occasionally seen. It is concluded that the tumor cells are of epithelial origin. It is suggested that the peripheral bronchi retain some of their embryonic capacities and that they again begin to produce alveolar epithelial cells upon exposure to a carcinogen.

7021 STROMA-FORMATION IN EPITHELIAL MALIGNANT TUMOURS. (Rus.) Nikolaev, A. A. (No affiliation given); Yagubov, A. S. *Ark. Patol.* 37(2):21-28; 1975.

The role of fibroblasts in stroma formation, the rearrangement of stroma of malignant epithelial human tumors, and the influence of the parenchymatous component of neoplasm on these processes was investigated by histological, histochemical, and electron-microscopic methods. Surgically removed carcinomas of the mammary gland (73 cases), lungs (56), and stomach (92) were used. The stroma was studied in the zone of infiltration and inside the tumor node. Multiplying epithelial elements of the tumor induced proliferation of histogenic and vascular fibroblasts. The active fibroblasts played a dual role either producing fibers and interstitial matter of tumorous stroma or participating in disintegration of preceding and newly formed collagenous structures. The processes of stroma formation complied with conventional schemes of normal fibrogenesis and rearrangement of the interstitial tissue. Fibroblasts of the tumor stroma formation complied with conventional schemes collagen. The authors suggest that in the course of the tumor growth, correlation between the parenchyma and stroma is maintained, the leading role being played by the epithelium.

7022 CELLULAR CHANGES IN THE BASALOID CELL PAPILLOMA. (Eng.) Lagerholm, B. (Dep. Dermatol., Karolinska sjukhuset, Stockholm, Sweden); Frithz, A.; Sant Orp, C. J. *Acta Derm. Venereol. (Stockh.)* 55(1):39-50; 1975.

Basaloid cell papillomas of the solid and papillomatous types from five patients were studied with the electron microscope. Some of the ultrastructural findings, e.g. an increased number of mitochondria, a certain mitochondrial polymorphism, the occurrence of irregularly shaped intracytoplasmic vesicles, the abundance of endoplasmic reticulum hypertrophy, and the remarkable presence of microtubule-like structures (an unusual finding in a material fixed at 18 C) are indicative of an altered metabolic activity. The alternating presence and absence of keratohyalin was found to be submicromorphologically related to the formation

of A- and B-cells, respectively. This is compared with the formation of parakeratosis in psoriatic lesions without keratohyalin. A formation of orthokeratosis as seen by the light microscopic procedure seems possible without the previous occurrence of keratohyalin.

- 7023 CELL SURFACE DIFFERENCES IN DUCTS FROM CANCEROUS AND NONCANCEROUS HUMAN BREASTS. (Eng.) Spring-Mills, E. (Veterans Adm. Hosp., San Francisco, Calif.); Elias, J. J. *Science* 188(4191): 947-949; 1975.

The surface morphology of ducts from cancerous and noncancerous human breasts was studied by scanning electron microscopy. Material obtained at biopsy or mastectomy from 32 women with the following breast abnormalities was observed: dysplasia (11), fibroadenoma (4), lobular carcinoma in situ (2), and infiltrating duct carcinoma (15). The surgical specimens were frozen, cracked, and critical-point-dried in liquid CO₂. The upper halves of ducts close to the surface of the dried tissue were teased away under a dissecting microscope to give an unimpeded view of essentially all cell surfaces bordering one half of the duct lumen. The apical surface of the duct epithelium from cancerous breast displayed some or all of the characteristics of ducts from noncancerous breasts. Duct cells from cancerous breasts, however, showed greater variation in size and shape and in the number, length, and arrangement of microvilli. Alterations which appeared to be specific for carcinomatous breasts are the following: 1) the partitioning of the surface microvilli into small groups or clusters composed of three or more microvilli clumped together at their tips; 2) the presence of intercellular microvillus contacts; and 3) a prominent clump of thickened, irregular microvillus-like projections in the center of the apical surface. Tissues from 19 women were processed and analyzed without knowledge of their clinical diagnosis; in every case, there was perfect agreement between the pathological diagnosis and the one made with the scanning electron microscope. It appears, therefore, that the distribution and arrangement of the apical microvilli on mammary duct epithelium may be a pathognomonic sign of carcinoma.

- 7024 SURFACE EPITHELIUM OF THE DEVELOPING OVARY: POSSIBLE CORRELATION WITH OVARIAN NEOPLASIA. (Eng.) Gundos, B. (Univ. California, San Francisco, Sch. Medicine, San Francisco, Calif. 94143). *Am. J. Pathol.* 81(2):303-320; 1975.

An ultrastructural analysis of the development of the surface epithelium in the human fetal ovary was performed, and possible mechanisms responsible for the observed proliferative changes are considered. Forty-two specimens (7-20 wk gestation) were obtained following therapeutic abortion and gonadal tissue dissected from the aborted fetus and processed for light and electron microscopic study. At 12-16 wk, light microscopy showed definite organization of the cortex into sex chords that resulted from the ingrowth

of connective tissue and blood vessels; there was a clear separation of the surface epithelium from the cortical cords. At 16-20 wk, marked proliferation of the surface epithelium together with increasing development of the tunica albuginea resulted in the formation of a thick surface epithelium in which multiple cell layers were present. The cellular arrangement was jumbled, and many different directions of orientation were evident. Nuclear infolding, pleomorphism, and nucleolar prominence were visible. Between 12-16 wk, electron microscopy showed slight nuclear changes in the epithelial cells. During 16-20 wk, the nuclei of the epithelial cells showed marked distortion, characterized by bizarre convolution, irregular infolding, deep grooves, and pseudolobulation. In some cases the irregularity gave the appearance of nuclear cavitation. Irregular chromatin distribution was evident, as was a general loss of polarity within the epithelium. Cytoplasmic and cell membrane features were similar to previous stages. The tunica albuginea was filled with fibroblasts, capillaries, and abundant collagen. The marked proliferation and associated nuclear changes in the fetal ovary produce a picture closely resembling that seen in surface epithelial neoplasms. The epithelial changes occur during the same time period that interstitial cells with ultrastructural and histochemical properties of steroid-secreting tissue appear in the ovarian stroma. Previous studies have shown high levels of glycolytic and NADPH-supplying enzymes as well as 3 β -hydroxysteroid dehydrogenase in the interstitial cells beginning in the fourth month. Although no conclusions can be drawn regarding the factors responsible for surface epithelial development in the fetal ovary or in ovarian tumors, the observation that proliferation in the fetal ovary occurs at the time that steroid-secreting cells differentiate in the ovarian parenchyma may be significant.

- 7025 MALIGNANT PHEOCHROMOCYTOMA OF THE BLADDER: THE LATE DEVELOPMENT OF RENAL CELL CARCINOMA. (Eng.) Deklerk, D. P. (Johns Hopkins Hosp., Baltimore, Md.); Catalona, W. J.; Nime, F. A.; Freeman, C. *J. Urol.* 113(6):864-868; 1975.

The case report of a 29-yr-old white man with an unusually late recurrence of a malignant bladder pheochromocytoma is presented. It came to clinical attention by the development of a renal cell carcinoma. The patient had hematuria and hypertension since he was 14. After diagnosis, the patient underwent a cysto-prostatectomy as well as resection of a satellite pheochromocytoma in the region of the left common iliac artery. He was normotensive postoperatively. In five years the hypertension recurred, becoming progressively more severe. An exploratory laparotomy was performed, and two lymph nodes containing metastatic pheochromocytoma were resected from the region of the bifurcation of the right common iliac artery. Seven years later there were no signs of pheochromocytoma, but the patient had flank pain and gross hematuria with nausea. Laboratory evaluation revealed microscopic hematuria with sterile urine. An excretory urogram revealed a mass lesion in the upper pole of the left kidney, and ar-

teriography disclosed vascular lesions in the upper pole of the left kidney and near the bifurcation of the left common iliac artery. At an exploratory laparotomy, a large mass was found in the upper pole of the left kidney and a 2 x 3 cm mass was found posterior to the left common iliac artery. A left radical nephrectomy was performed, and the lesion near the iliac artery was resected. Cells with tubular papillary structure characteristic of renal cell carcinoma were found in kidney mass. The histological picture of the latter lesion was that of a pheochromocytoma and was similar to the previously resected pheochromocytoma of the bladder. The finding of pheochromocytoma within lymph nodes appears to distinguish this pheochromocytoma as malignant. However, the latent period of 14 yr suggests that host defense mechanisms were remarkably effective in controlling the tumor. Cases of association of other primary neoplasms with pheochromocytomas may represent examples of von Hippel-Lindau disease with incomplete penetrance.

- 7026 TRANSPLANTABLE STRAINS OF URINARY BLADDER CANCER AND HEMANGIOPERICYTOMA OBTAINED BY ECTOPIC TRANSPLANTATION OF FETAL URINARY BLADDER TISSUES. (Rus.) Osipova, T. V. (Inst. Experimental Clinical Oncology, Acad. Medical Sci., Moscow, USSR); Svet-Moldavskii, G. Ia.; Turusov, V. S. *Vopr. Onkol.* 21(9):89-93; 1975.

Minced urinary bladder tissues from CBA x C57B 1/6j fetuses and BalB/C female mice were s.c. injected into syngeneic male recipients. Over a fifteen month period, multichambered urinary bladder cysts, up to 20 x 20 mm in size, and lined with epithelium and filled with secretion developed in all mice. Cysts from the CBA x C57B 1/6j group were sc injected into syngeneic recipients, and seven months later, a slow-growing, poorly-differentiated, transitional-cell carcinoma spontaneously developed in one recipient. In one hybrid mouse with a urinary bladder cyst, a huge tumor developed within the bone of the femur. After a series of passages, this tumor was identified as a hemangiopericytoma, although it is unclear whether its development was spontaneous or induced by the growing urinary bladder cyst. Thus, transplantable strains of urinary bladder cancer and hemangiopericytoma were obtained.

- 7027 ON PATHOGENETIC RELATIONSHIPS BETWEEN CARCINOMA OF THE URINARY BLADDER AND DISEASES OF THE SPINAL CORD. (Ger.) Schnoy, N. (Pathologisches Institut der Freien Universität im Klinikum Westend, 1 Berlin 19, Spandauer Damm 130, Germany); Leistenschneider, W. *Med. Monatsschr.* 29(3):133-135; 1975.

The possibility of primary malignant tumors of the urinary bladder being a late complication in chronic diseases of the spinal cord is demonstrated in two cases. Funicular myelosis with pernicious anemia

and progressing paraplegia were followed after 21 yr by the manifestation of a carcinosarcoma of the bladder in a 70-yr-old man. Recurrent infections of the urinary tract after traumatic paralysis of both legs were followed by the manifestation of squamous epithelial carcinoma after 23 yr in a 57-yr-old man. Chronic recurrent urocystitis leads to the destruction of the epithelium and finally to hyperplastic and leukoplakia-like epithelial transformations, which predispose to carcinoma formation. The initial functional disturbances of the bladder may originate from degenerative or traumatic lesions of the spinal cord.

- 7028 SPIRONOLACTONE BODIES IN AN ADRENAL ADENOMA. (Eng.) Shrago, S. S. (UCLA Sch. Medicine, Los Angeles, Calif. 90024); Waisman, J.; Cooper, P. H. *Arch. Pathol.* 99(8):416-420; 1975.

The history of a patient with an adrenal adenoma and hyperaldosteronism is presented, and the light and electron microscopic features of the adenoma are described. The 47-yr-old man had been placed on spironolactone (100 mg, three times per day) following the diagnosis of hyperaldosteronism. The treatment was continued for two months, after which an enlarged left adrenal gland was removed. Light microscopic examination of the adrenal adenoma revealed spironolactone bodies. Electron microscopy revealed that at the periphery of these bodies, their membranes were continuous with the smooth endoplasmic reticulum, suggesting derivation from this organelle. Examination of the mitochondria disclosed no whorled cristae or intramitochondrial deposits. A previously published study on rats suggested that spironolactone bodies are derived from whorled cristae within the mitochondria. These spironolactone bodies have been described in the adrenal cortex only in patients who have received spironolactone; the pharmacologic specificity of the bodies strongly suggests a direct mode of action by spironolactone on aldosterone production by cells of the adrenal zone glomerulosa.

- 7029 URINARY LITHIASIS AND PARATHYROID ADENOMA. (Fre.) Colas, J. -M. (Service d'Urologie, C.H.U., 25000 Besancon, France); Dupond, J.-L.; Saint-Hillier, Y.; Darcq, E.; Bittard, M. *J. Urol. Nephrol. (Paris)* 81(6):419-423; 1975.

In a series of 400 patients with calcium lithiasis seen over a period of 3 yr, 11 were attributable to parathyroid adenomas and 6 to parathyroid hyperplasias. An additional five adenomas of the parathyroid occurred without urinary lithiasis. Of the 11 cases in this series, eight had been operated several times for lithiasis. The average time between the first nephrotic pain and the discovery of the adenoma was six years. Hypercalcemia was the most constant symptom and the average level was 117 mg/l. All parathyroid tissue should be located

since multiple adenomas are found in 6% of cases of often diffuse hyperplasia. After surgery, there was a significant fall in the blood calcium levels; in three cases, a temporary tetanus-like crisis required calcium therapy. Renal function was completely restored and urinary infection cleared. It was not always necessary to remove the calcium calculi. Hyperparathyroidism should be suspected in all cases of calcium lithiases, particularly if they are bilateral and recurrent. The authors suggest detection of adenoma or hyperplasia of the parathyroid to prevent development of renal insufficiency.

- 7030 THE LUNGS IN LYMPHANGIOMYOMATOSIS AND IN TUBEROUS SCLEROSIS. (Eng.) Stovin, P. G. I. (Papworth Hosp., Papworth Everard, Cambridge, England); Lum, L. C.; Flower, C. D. R.; Darke, C. S.; Beeley, M. *Thorax* 30(5):497-509; 1975.

Histories are presented for two female patients with pulmonary lymphangiomyomatosis and one of tuberous sclerosis with pulmonary involvement; and 33 previously published cases of lymphangiomyomatosis and 29 of tubular sclerosis are reviewed. In the lymphangiomyomatosis cases, one woman who had experienced her first spontaneous pneumothorax at age 26, followed by further bilateral pneumothoraces the next year died at 31 of intractable respiratory failure. She had had a lymphopenia with a fluctuating eosinophilia for the last three years of her life. At necropsy, anomalous pulmonary veins (3 mm diameter) were found in each upper lobe. The pleural cavities were obliterated, and cystic spaces were seen on serial slicing of the lungs. A spongy mass was seen around the inferior vena cava and the right common iliac vessels. The second case was first seen at age 33 with pulmonary symptoms which worsened. Four years later, centrifugation of the milky pleural fluid showed chylomicra on the surface. The lung surface was covered with 3 mm cysts. The chylothorax did not recur, but the patient began to expectorate chyle, a condition which continued until her death. At necropsy, a retroperitoneal lymphangiomyoma was seen adjacent to the right ureter together with chylous serous effusions. The third case was a mentally defective woman diagnosed as having tuberous sclerosis. There were no complaints referable to the respiratory system except for slight dyspnea. She died at 59 in congestive cardiac failure having shown moderately increasing dyspnea. Microscopically, the lungs showed small alveolar cysts up to 5 mm diameter. Focal leiomyomata were present in the elastic and larger muscular pulmonary arteries. The 33 published cases of lymphangiomyomatosis consist only of female patients, and chylothorax has been reported in 26 of the 33. Chylothorax was not mentioned in 29 cases (27 female, 2 male) of tuberous sclerosis. Spontaneous pneumothorax and hemoptysis were seen in both conditions. The composition and distribution of the lesions were different in the two disorders: lymphangiomyomatosis involved lymphatics both intra- and extra-nodal in the central part of the body, while tuberous sclerosis involved mesodermal disorders affecting the body

both centrally and peripherally. It is suggested that lymphangiomyomatosis and tuberous sclerosis are two different disorders.

- 7031 SPONTANEOUS REGRESSION AND LEUKODERMA IN MALIGNANT MELANOMA. (Ger.) Happle, R. (Universitäts-Hautklinik Münster D-4400 Münster von-Esmarch-Strasse 56 Bundesrepublik Deutschland); Schotola, I.; Macher, E. *Hautarzt* 26(3):120-123; 1975.

Four cases of superficially spreading malignant melanoma with partial spontaneous regression and/or leukoderma in four patients (3 men and 1 woman), aged 27-61 yr, are reported. Partial spontaneous regression was observed in three cases. Leukoderma was found in three cases, including two with the leukoderma localized in the center of the melanoma. In these two cases, leukoderma was interpreted as being the result of the defense mechanisms against the melanoma cells. Halo nevus-type peripheral leukoderma, observed in one case, indicated an immunological relationship between malignant melanoma and principally benign halo nevus. Remote leukoderma with inflammatory infiltrate, coinciding with the partial spontaneous regression of the melanoma, seems to suggest a pathogenic relationship between malignant melanoma and leukoderma. Partial spontaneous regression and coincident leukoderma do not project favorable prognoses.

- 7032 A CASE OF CARCINOMA WHICH WAS SUPERIMPOSED ON AN ANOMALY OF THE TRACHEAL BRONCHI. (Bul.) Uchikov, P. (Med. Acad., Plovdiv, Bulgaria); Nikolov, P. *Khirurgia (Sofia)* 27(4):318-320; 1974.

A case study of a 58 yr-old woman with carcinoma of the right side of the pleuritic cavity developing from the tracheal bronchi is presented. A tumor the size of an orange was surgically removed and histological analysis demonstrated alveolocellular cancer. No enlarged lymphs were found in the chyle. There were no postoperative problems.

- 7033 SQUAMOUS CELL CARCINOMA OF BOTH EARS ASSOCIATED WITH HYPERCALCAEMIA. (Eng.) Armati, R. P. (Park House, 187 Macquarie St., Sydney, N.S.W. 2000 Australia); Brooks, J. S.; Corlette, P. M. C. *Med. J. Aust.* 2(6):218-222; 1975.

The case report of a 54-yr-old man showing rapid destruction of both ears by squamous cell carcinoma is presented. The bilateral nature and size of the lesions were unusual. The speed of growth was very rapid for skin cancer. Solar damage was not marked, although there were some small hyperkeratoses on the hands. There was no history of irradiation of the

ears or exposure to any carcinogen. The only major trauma was frostbite thirty years earlier. The long interval between the frostbite and the onset of symptoms was noteworthy, and it is suggested that in the majority of cases several etiological factors are at work either successively or simultaneously. The patient presented hypercalcemia associated with slight lowering of the serum alkaline phosphatase level which fell on the eighth day of radiotherapy, reaching normal levels within 2 wk. No other significant treatment was given. No record was found of a nongenital skin cancer associated with hypercalcemia, and it is suggested that this patient's ear lesions secreted a bone mobilizing substance.

- 7034 **GANGLIONEUROMAS IN HAMSTERS.** (Eng.) Rustia, M. (Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, Nebr. 68105); Cardesa, A. *Acta Neuropathol. (Berl.)* 32(4):325-331; 1975.

Three ganglioneuromas occurring in Syrian golden hamsters under two different experimental settings with ethylnitrosourea precursors are described: previously reported cases in this species are reviewed; and the histogenesis of such tumors is discussed. The three ganglioneuromas were found incidentally among other pathological alterations during autopsies. Two of the animals in which ganglioneuromas were found had received ethylurea and sodium nitrite simultaneously during their adult lives. The third case was in an animal that had been prenatally exposed to the same chemicals. Two of the tumors were in the vertebral thoracic region, originating in the sympathetic chain; the third originated from the celiac ganglion. The neoplastic tissue of the ganglioneuromas consisted of mature ganglion cells, varying amounts of neurofibrils, and stroma. The ganglion cells were distributed singly, haphazardly or in compact clusters and had abundant pink, acidophilic cytoplasm, with occasional overtones of basophilia. The neurofibrils appeared as subtle, delicate fibrils, arranged in an interlacing pattern or loosely in bundles throughout the neoplastic tissue. The bulk of the neoplastic tissue consisted of stroma in which cellular elements apparently of Schwann cell origin were loosely distributed in the fibrillary matrix. These cells had round or oval, often hyperchromatic, nuclei and undefined cytoplasm. They frequently underwent microcystic degeneration. A survey of reports on spontaneous and experimentally induced tumors in hamsters failed to reveal any spontaneous occurrence of these neoplasms; they were reported only in association with exposure to powerful carcinogenic agents. The three ganglioneuromas in this study are thought to have been induced by ethylnitrosourea because this carcinogenic agent has a great affinity for neural tissue in general; it also has the potential for the induction of peripheral nervous system tumors, particularly in hamsters. Ganglioneuromas may originate from mature ganglion cells under the action of various chemical carcinogens, especially when initiated by carcinogenic stimulation with a strong neurotropic agent such as ethylnitrosourea.

- 7035 **ARGYROPHIL CELL CARCINOMAS (APUDOMAS) OF THE UTERINE CERVIX: LIGHT AND ELECTRON MICROSCOPIC OBSERVATIONS OF 5 CASES.** (Eng.) Tateishi, R. (Cent. Adult Dis., Osaka, Japan); Wada, A.; Hayakawa, K.; Hongo, J.; Ishii, S.; Terakawa, N. *Virchows Arch. [Pathol. Anat.]* 366(4):257-274; 1975.

During a two-year period, invasive carcinomas of the uterine cervix from 97 patients were studied by light microscopy. Of these, five had argyrophil tumor cells. The ages of the five patients ranged from 36-49 yr with a mean age of 42.2 yr. The morphological features of these five tumors were consistent with those of a variety of endocrine polypeptide neoplasms including thyroid medullary carcinomas, carcinoids, pancreatic islet-cell tumors, and oat cell carcinomas of the lung. Microscopically, the tumors were characterized by the formation of solid-sheets, ribbons, streams, and rosettes. They were characterized electron microscopically by the presence of neurosecretory-type granules, the abundance of intracytoplasmic microfilaments, the absence of tonofibrils, and the paucity of desmosomal attachments. On the basis of the microscopic, electron microscopic, and cytochemical characteristics, it is suggested that the tumors are a specific type of cervical carcinoma derived from the argyrophil cells, normally found among the linings of the endocervical glands and the cervical squamous epithelium. Because of this, these tumors should be regarded as endocrine tumors and members of the apudomas.

- 7036 **HUMAN BRAIN IN TISSUE CULTURE. IV. MORPHOLOGICAL CHARACTERISTICS.** (Eng.) Rorke, L. B. (Mult. Scler. Res. Cent. Wistar Inst., Philadelphia, Pa.); Gilden, D. H.; Wroblewska, Z.; Santoli, D. *J. Comp. Neurol.* 161(3):329-339; 1975.

Morphological and staining characteristics of cells from normal and diseased brains and PML-SV40-transformed cultures established from 48 explants of adult human brain from 19 biopsy or autopsy cases were investigated. Cells were suspended in Eagle's medium plus 10% fetal calf serum (FCS) and seeded onto glass cover slips, fed with 5 ml Eagle's medium plus FCS, and incubated at 37 C until 50-100% confluent. They were washed three times in phosphate buffered saline and fixed in four different fixatives: 1) 10% neutral buffered formalin for 1-24 hr for hematoxylin and eosin, cresyl violet and Bodian stains; 2) Zenker's for 1 hr for phosphotungstic acid hematoxylin stain; 3) Bouin's solution for 1 hr for the trichrome and Lendrum stains; and 4) formalin ammonium bromide for 24 hr for the Cajal gold chloride method. Cover slip preparations of normal and transformed cells from different areas of the brain as well as from ependyma, choroid plexus and optic nerve were stained. Tissue culture preparations were also monitored by the indirect fluorescent antibody staining method for glial fibrillary acid (GFA) protein. There was no basic difference between cell types which grew out from normal and diseased brains. At least seven types of cells were distinguishable, four apparently

of mesenchymal origin and designated PG (polygonal), EL₁ and EL₂ (elongated) and MB (mesoblastic cells) and three probably derived from neuroglia and designated TL₁, TL₂ (triangular) and EL₃. Identification of cell types by differential staining techniques was not possible because of inconsistent staining characteristics. Identification was based, therefore, on general morphological characteristics, on comparison with the well-established fibroblastic cell line, WI38, and on the indirect fluorescent antibody staining method for recognition of GFA protein. Most of the transformed brain cells lost their distinctive morphological features. Mitotic figures abounded and cell growth was luxurious. Nuclei were frequently gigantic, multilobulated and bizarre. Few eosinophilic, intracytoplasmic inclusion bodies were seen in normal brains, a larger number were present in some of the brains from neurologically impaired patients, and they abounded in the transformed cells. It is pointed out that cells in culture do change their morphological characteristics and that the interpretation of the origin of brain cells maintained in culture should be considered with this fact in mind.

- 7037 THE ULTRASTRUCTURE OF A FEMINIZING GRANULOSA-THECA TUMOR. (Eng.) Waisman, J. (Center Health Sciences, Univ. California, Los Angeles, Calif. 90024); Lischke, J. H.; Mwasi, L. M.; Dignam, W. J. *Am. J. Obstet. Gynecol.* 123(2):147-150; 1975.

The ultrastructure and histochemistry of a tumor removed from the right ovary of a 13-yr-old girl with evidence of hyperestrinism was studied. This neoplasm was composed predominantly of granulosa cells and exhibited some changes of luteinization. The neoplastic cells displayed an investment of basement membrane material which was closely related to fibrillar collagen within the tumor. Scattered throughout the neoplasm were small numbers of cells with characteristics of the theca, and a few cells had cytoplasmic features suggestive of smooth muscle. The ultrastructural findings of eight similar tumors have been described. The production of large amounts of basement membrane material, observed in the case described, is a unique feature of granulosa-theca tumors. The results indicate an intimate spatial relationship between the basement membrane material and collagen fibers in the tumor, suggesting a bond between the two.

- 7038 ULTRASTRUCTURE OF PITUITARY TUMOR CELLS: A CRITICAL STUDY. (Eng.) Olivier, L. (Laboratoire D'Histologie-Embryologie [CNRS ERA 42], Faculte de Medecine, Pitie-Salpetriere, Paris, France); Vila-Porcile, E.; Racadot, O.; Peillon, F.; Racadot, J. *Ultrastruct. Biol. Syst.* 7:231-276; 1975.

The features of spontaneous and experimental tumors were compared to those of normal pituitary cells, and related to normal pituitary cell cytogenesis

in the fetal and adult pituitary. Pituitary tumors show various biological and cytological aspects related to their "spontaneous" or "induced" origin. Spontaneous tumors, either functional (secreting) or nonfunctional, are only disclosed at a well-developed stage; they appear relatively stable during their evolution in the absence of endocrine disturbances. Three main categories of functional tumors were described: tumors in acromegaly involving the somatotroph function, tumors in Cushing's disease involving the corticoadrenotroph function, and tumors in amenorrhea-galactorrhea involving the mammatroph function. Nonfunctional human adenomas consist of cells that are chromophobe under the light microscope, but under the electron microscope show a few small granules. Experimental tumors differ from human tumors since they undergo successive biological and cytological transformations during their evolution, beginning with an endocrine disturbance that induces the stimulation of one secretory function and later developing autonomous and malignant characteristics. When autonomy is attained, the functional capacities are modified and new hormonal secretory capacities may arise. Such changes are associated with chromosome modification, stressing the transformed nature of the cells. The authors suggest that these alterations may result from the selection of variant cell clones which possess a reproductive advantage.

- 7039 EPITHELIAL LIVER HAMARTOMA, SYSTEMIC ARTERIAL HYPERTENSION AND RENIN HYPERSECRETION. (Eng.) Cox, J. N. (Dep. Pathol., Univ. Geneva, Switzerland); Paunier, L.; Vallotton, M. B.; Humbert, J. R.; Rohner, A. *Virchows Arch. [Pathol. Anat.]* 366(1):15-26; 1975.

The case of a 14-yr-old girl with a voluminous epithelial liver hamartoma, presenting with hypertension and high serum renin levels, is documented. Initial manifestations included severe headaches, vomiting, Kernig and Brudzinski signs, and arterial hypertension. Serum electrolytes, blood glucose, and urea nitrogen were normal; serum glutamate-pyruvic transaminase (SGPT) was initially normal, then became elevated (151 mEz/l), while plasma renin activity (PRA) was quite elevated at 5.71 ng/ml/hr. A voluminous greenish yellow tumor 21 cm in diameter was removed during right liver lobe resection. Histologic examination disclosed a tumor with numerous large regenerative nodules; the mass outside the necrotic area was characterized by cords and tubules of well differentiated liver cells, cells of fine granular cytoplasm, irregular glycogen distribution, and prominent nucleoli. The normal lobular architecture of the liver was absent, and a dilatation of the portal vein and its tributaries was found within the normal liver parenchyma. The histological appearances in the case were consistent with those of an epithelial hamartomatous lesion or adenoma. The dominant manifestation of arterial hypertension was associated with high plasma renin activity prior to removal of the tumor. Blood from the hepatic vein had more plasma renin activity than peripheral blood. These two findings suggest

that the existing liver tumor was the site of renin production. The plasma renin activity was 5-20 times normal preoperatively, but returned to normal within 9 days after surgery. These results further support the view that abnormal renin production was responsible for the systemic arterial hypertension.

- 7040 ULTRASTRUCTURE OF HUMAN BRONCHIOLO-ALVEOLAR CELL CARCINOMA. (Eng.) Bedrossian, C. W. M. (Baylor Coll. Medicine, 1200 Moursund Ave., Houston, Tex. 77025); Weilbaecher, D. G.; Bentnick, D. C.; Greenberg*, S. D. *Cancer* 36(4):1399-1413; 1975.

- 7041 RETARDED DEGENERATION OF AN ANCIENT CAUSTIC STENOSIS OF THE MIDDLE THIRD OF THE ESOPHAGUS. (Fre.) Guillard, J. (15, rue St-Maur, 76000 Rouen, France); Bezier, J.; Metayer, J. *Sem. Hop. Paris* 51(23):1539-1541; 1975.

- 7042 LATE OCCURRENCE OF PRECANCEROUS CHANGES AND CARCINOMA OF THE GASTRIC STUMP AFTER BILLROTH II RESECTION. (Eng.) Domellof, L. (Departments Surgery and Pathology, Univ. Umea, Umea, Sweden); Eriksson, S.; Janunger, K.-G. *Acta. Chir. Scand.* 141(4):292-297; 1975.

- 7043 EVALUATION OF ENDOSCOPIC EXAMINATION OF COLON TUMORS IN RATS. (Eng.) Narisawa, T. (American Health Foundation, Valhalla, N.Y.); Wong, C.-Q.; Weisburger*, J. H. *Am. J. Dig. Dis.* 20(10):928-934; 1975.

- 7044 ADENOMATOID TUMORS (MESOTHELIOMA) OF TESTICULAR AND PARATESTICULAR TISSUE. (Eng.) de Klerk, D. P. (601 North Broadway, Baltimore, Md. 21205); Nime, F. *Urology* 6(5):635-641; 1975.

- 7045 CARCINOMA OF THE PANCREAS IN RATS (IMPLANTATION TESTS). (Ger.) Klemm, V. G. (Bereich Medizin, Universität Rostock, East Germany); Mehnert, W. H. *Z. Gesamte Inn. Med.* 30(13):452-454; 1975.

- 7046 LEUKOPLAKIA BUCCALIS: AN ENIGMA. (Eng.) Cooke, B. E. D. (Welsh Natl. Sch. of Medicine, Heath Park, Cardiff, CF4 4XN, England). *Proc. R. Soc. Med.* 68(6):337-341; 1975.

- 7047 NEW DATA ON OLIGOBLASTIC LEUKEMIAS (OBL): ANALYSIS OF 120 CASES. (Fre.) Izrael, V. (Unité de Chimiothérapie, Institut de Recherches sur les Leucémies et les maladies du sang, C.H.U. Saint-Louis, 2, place du Dr-Fournier, F 75475 Paris Cedex 10, France); Jacquillat*, C.; Chastang, C.; Weil, M.; de Heaulme, M.; Boiron, M.; Bernard, J. *Nouv. Presse Med.* 4(13):947-952; 1975.

- 7048 MYOCLONIC ENCEPHALOPATHY AND NEUROBLASTOMA. (Eng.) Delalieux, C. (Hopital Universitaire St. Pierre, Brussels, Belgium); Ebinger, G.; Maurus, R.; Sliwowski, H. *N. Engl. J. Med.* 292(1):46-47; 1975.

- 7049 ULTRASTRUCTURAL ASPECTS OF ACUTE PROMYELOCYTIC LEUKEMIA. (Spa.) Rozman, C. (Escuela de Hematología "Farreras Valenti," Facultad de Medicina, Casanova, 143, Barcelona-11, Spain); Woessner, S. *Sangre (Barc.)* 20(2):150-160; 1975.

- 7050 PATTERNS OF METASTASES IN VIRAL AND CHEMICAL LEUKEMIAS: IMMUNOLOGIC CORRELATIONS [abstract]. (Eng.) Ioachim, H. L. (Lenox Hill Hosp., New York, N.Y.); Pearse, A.; Keller, S. *Proc. Am. Assoc. Cancer Res.* 16:106; 1975.

- 7051 SURFACE ULTRASTRUCTURAL CHANGES OF LYMPHOID CELLS IN CHRONIC LYMPHOCYTIC LEUKAEMIA. (Eng.) Brynes, R. K. (Dept. Pathol., Univ. Chicago, Ill.); Hamburg, A.; Reese, C.; Golomb, H. M. *Lancet* 1(7908):687-688; 1975.

- 7052 DEPOSITS OF IMMUNOGLOBULINS IN THE CELLS OF CHRONIC LYMPHATIC LEUKEMIA. (Ger.) Huhn, D. (Inst. Hamatologie, D-8000 München 2, Landwehrstr. 61, West Germany); Thiel, E.; Rodt, H. *Klin. Wochenschr.* 53(7):317-320; 1975.

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See also:

- * (Rev): 6631, 6632, 6633, 6635, 6637, 6639, 6646, 6657, 6661, 6662
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- * (Phys): 6807, 6827
- * (Viral): 6846, 6899, 6908
- * (Immun): 6975, 6993
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- 7109 A TEN YEAR STUDY OF OVARIAN TUMORS.
(Eng.) Yaker, A. (Sch. Med., Univ. California, San Diego); Benirschke, K. *Virchows Arch. [Pathol. Anat.]* 366(4):275-286; 1975.

Two hundred and thirteen ovarian tumors taken from 204 patients over a ten-yr period were diagnosed histologically and grouped according to recommendations of the World Health Organization. Common epithelial tumors were the most frequent neoplasms of the ovary. The commonest lesion was the serous type, comprising 41.3% of tumors. Half of the tumors from this histologic phenotype were malignant, being cystic, papillary and well differentiated. Mucinous tumors represented 12.6% of the total tumors and are considered to be of "epithelial origin". Only four endometrioid carcinomas were found (1.8%). Sex cord stromal tumors formed the smallest group in this series. Germ cell tumors comprised 25.3% of the series. Secondary ovarian tumors comprised 10.8%. The patients involved were 15-86 yr old. The peak incidence occurred in patients 40-70 yr old. Dermoid cysts were the most frequent among young women; cystadenocarcinomas were more common in patients over 40. The age at which the incidence of serous cystadenoma and adenofibroma was highest occurred in the 50's; this was also true for the less frequent mucinous adenocarcinoma. There were 107 benign and 93 malignant tumors. Of the benign tumors, 64 were ovarian tumors in the patients under 40. Seventy-seven malignant tumors were in patients over 40, implying that 82% of all malignant tumors were removed from women who were at least 40 yr old. The site of involvement was recorded in 181 tumors, of which 25% were bilateral. Definite silicate crystals were found in only five of 52 adhesions observed in 152 patients. The relative paucity of this finding is in disagreement with the previous finding of such material in other gynecologic specimens, and may reflect the fact that normal ovarian tissue was not recognized in 61 cases. It was thus impossible to identify ovarian adhesions. That there is a direct response by epithelial cells to silicates, transforming these cells to malignant types is speculative. Although the crystalline material may be so small that it is beyond the limit of the optical microscope, the minimal incidence of larger crystalline material detected here denies a direct relationship between silicate and the development of ovarian cancers.

- 7110 THE EPIDEMIOLOGY OF CANCER OF THE PROSTATE [editorial]. (Eng.) Higgins, I. T. T. (Sch. Public Health, Univ. Michigan, Ann Arbor, Mich. 48104). *J. Chronic Dis.* 28(7/8):343-348; 1975.

Epidemiological aspects of prostatic cancer are reviewed. The incidence of this form of cancer increases steadily with age from about 40 yr and varies internationally, as does the mortality rate. Since migration appears to influence the liability to the clinical disease, environmental factors may be important in its expression. Cancer of the prostate is also related to marital status in that mortality rates for cancer of the prostate are lowest in single persons and highest in the widowed and divorced; the

increased incidence rates among the married may be mainly in those with children. Although sexual factors may be important, there have been few investigations into sexual practices in relation to prostatic cancer. Heredity may also be important, but neither socioeconomic circumstances nor occupational exposures show a consistent relationship with cancer of the prostate. Although much of the biochemical evidence is contradictory, cancer of the prostate is often thought of as a hormone-dependent cancer; this is partly because of the experimental demonstration of regression following castration or estrogen therapy and partly because of the finding at autopsy of multiple endocrine changes. The relationship of benign prostatic hyperplasia (BPH) to cancer of the prostate is controversial. A prospective study of 345 patients with BPH who were admitted to Roswell Park Memorial Institute between 1945 and 1965, and a retrospective study of 290 patients with prostatic cancer indicated an increased risk of prostatic cancer from BPH. These findings were, however, at variance with those of an investigation of 838 men who had had subtotal prostatectomy at Boston's Lahey Clinical Foundation between 1940 and 1959. The discrepancy may have been due to the elimination of latent disease from the case group but not from the control group in the Lahey Clinic study. Elucidation of the etiology of prostatic cancer requires close team work of epidemiologists, pathologists, nutritional biochemists, and steroid chemists concentrating primarily on the differences in cancer in Caucasians, Negroes, native Japanese, and immigrants to the United States.

- 7111 END RESULTS OF BREAST CANCER PATIENTS IN FINLAND 1953-1968. (Fin.) Hakama, M. (Suomen Syöpärekisteri, 00170 Helsinki 17); Riihimäki, H.; Saxen, E. *Duodecim* 91(5):266-277; 1975.

The material consists of 12125 female breast cancer patients reported to the Finnish Cancer Registry during 1953-1968. Treatment was considered to be any procedure performed on the patient in the first four months after cancer determination, and was divided into surgery, radiotherapy, combination of surgery and radiotherapy, and other treatment. The patients were divided into three age groups: women under 50, 50-64, and over 65 yr of age, with localized or metastasized tumors. Two-thirds of the patients received a combination of surgical and radiation treatment, only a fifth were treated only surgically. In 47.1% of the cases the tumor was local; 31.5% of the patients were under 50 yr, 38.9% were 50-64, and 29.5% were over 65 yr of age. In the 50-64 year age group there were considerably more nonlocalized tumors, but in the other age groups the ratio was about even. One-half of all patients lived five years. One half of those with a non-localized or metastasized tumor, lived three years. Median survival was ten years, if the tumor was local. The five-year survival improved five percentage points in the 1960's. The difference in survival of patients receiving different treatment methods was small. The death rate of patients who were treated only with radical surgery, was the same for several years toward the end of the observation

period as that of normal Finnish women of corresponding age, whereas the death rate of patients who received combined surgery and radiotherapy surpassed that of the other patients the longer they lived, and at the end of the observation period had the highest death rate, whether the tumor was localized or not. Short term death rates for these patients was lower, however. The typical treatment of breast cancer in Finland is a combination of surgery and radiotherapy, although the trend is toward a treatment where radiotherapy is prescribed only when the tumor has spread. Despite differences in methods of treatment the results in Finland are of the same class as in the U.S., which strengthens the opinion that treatment has only a secondary effect on prognosis as compared with the characteristics of the tumor.

- 7112 PAPILLARY THYROID CARCINOMA IN DENMARK, 1943-1968. (Eng.) Lindahl, F. (Danish Cancer Registry, Inst. Cancer Epidemiology, Copenhagen, Denmark). *Cancer* 36(2):540-552; 1975.

All cases of papillary thyroid carcinoma (TC) diagnosed in Denmark from 1943 to 1968, including those based on postmortem examinations were studied. Direct comparison with clinical data from hospitals elsewhere will therefore tend to show less favorable results. In general, Danish cases show a higher average age than those from American hospitals. For the younger age groups this may be because therapeutic x-irradiation of the thymus during childhood has never been practiced in Denmark. However, the later occurrence in life of Danish cases and the less favorable prognosis suggest failure to realize the malignant character of the lesion in the earlier part of its course, and a variable experience on the part of the surgeons and the institutions from which the material was collected. In 25 of 79 unoperated patients (6%) the diagnosis of TC was made post-mortem. TC was the cause of death in only a few of these cases. The age-adjusted incidence rate, the mortality, and complications are discussed. The prognosis may be improved by more extensive operations on the thyroid gland, avoiding complications such as paralysis of the recurrent laryngeal nerve and tetany. The surgical efforts should be supplemented with suppression of the TSH production. Prospective studies of papillary TC should be established on an international basis.

- 7113 THE EPIDEMIOLOGY OF ESOPHAGEAL CANCER IN NORTH CHINA AND PRELIMINARY RESULTS IN THE INVESTIGATION OF ITS ETIOLOGICAL FACTORS. (Eng.) Anonymous. (The Co-ordinating Group for Res. on the Etiology of Esophageal Cancer of North China). *Sci. Sinica* 18(1):131-148; 1975.

The incidence and mortality rates of esophageal cancer, including cancer of the gastric cardia, are high in the areas of North China, where in some counties it is ranked as the primary cause in the total death rate. An epidemiological survey of esophageal cancer was done covering 1969-1971. The area with high mortality rate of esophageal

cancer is located in the southern parts of the Taihang Mountains on the borders of Honan, Shansi, and Hopei provinces. From this area extending out like irregular concentric belts, the mortality rates decreased gradually. The highest age-sex adjusted mortality rate reached 139.80/100,000 and the lowest rate was 1.43/100,000, with an average mortality rate of 37.39/100,000. The ratio of male to female patients was on the average of 1.6 to 1. The higher the mortality rate of a locality, the lesser was the difference in its sex ratio. Over 60% of the total mortality rate was in the age groups 50-69 yr. In counties with a high incidence of the esophageal cancer there were also a greater number of people suffering from epithelial dysplasia of the esophagus. The average age-sex adjusted incidence-rate of esophageal cancer of Linhsien county (1959-1970) was 108.56/100,000, and the mortality rate was 99.76/100,000. The mortality rates showed little change during the past 30 yr. The ratio of esophageal cancer to cancer of the gastric cardia was 3 to 1. Most cases of cancer were located at the level of mid and lower third of the esophagus. In areas of high incidence of esophageal cancer among human beings, this cancer was also common among chickens and vice versa. Trace elements in the soil and drinking water, nitrosamines, secondary amines, nitrite and nitrate contents in food items, and fungus contamination in food were analyzed for comparative values in high and low incidence areas. Vitamin C reduced the urinary nitrites of 27 Linhsien women. Vitamin A reduced esophageal hyperplasia caused by methylbenzyl nitrosamine in Wistar rats.

- 7114 PANEL ON EPIDEMIOLOGY AND ETIOLOGY OF LARYNGEAL CARCINOMA. (Eng.) Hiranandani, L. H. (Madameama Road, Bombay 400001, India). *Laryngoscope* 85(7):1197-1207; 1975.

Observations over a 25 year period on epidemiology of cancer of the larynx in India are reported. In India, tobacco is used habitually in several forms. Higher economic classes in urban areas smoke cured tobacco in the form of cigarettes or cigars whereas the poor, rural population is more likely to smoke "Bidi", and uncured tobacco. Tobacco is also chewed or used as snuff. Laryngeal cancer is associated with smoking, either of cured or uncured tobacco. The incidence is ten times as great in men as in women, consistent with fact that only a small percentage of women smoke. Cancer of the oral cavity, which affects men and women equally, can be attributed to the use of a mixture of tobacco, slaked lime, betel nut and catechu chewed by both sexes. Leukoplakic changes in the mucosa of the oral cavity are associated with cancer of the oral laryngeal area. A study of 1,000 smokers revealed 10% with leukoplakic changes after smoking 10-20 cigarettes per day for three to four years, and 20 of these subjects developed laryngeal cancer within three years. Of 30% with no evidence of leukoplakia after consumption of 30-40 cigarettes per day for 10 to 50 years, only two developed cancer in the same time period. The remainder of the subjects in the study showed varying degrees of leukoplakia. Laryngeal

cancer, predominantly squamous cell carcinoma in India, does not appear to be related to factors of climate or genetics or to religious or social customs. The industrialized city of Bombay does not have a higher incidence than rural area. Prolonged diet deficiency, particularly of protein, may be a contributing factor.

- 7115 SOME FEATURES OF THE EPIDEMIOLOGY OF CANCER OF THE LARYNX IN AUSTRALIA AND PAPUA, NEW GUINEA. (Eng.) Atkinson, L. (Inst. Radiotherapy, Prince of Wales Hosp., Sydney, Australia). *Laryngoscope* 85(7):1173-1184; 1975.

Incidence of cancer of larynx in Australia, a country with an advanced technology and high standard of living, is compared with incidence in Papua, New Guinea where the majority of the population live in rural areas unchanged for thousands of years. In 1972, New South Wales with the largest population in Australia reported 3.7% of a total of 3,786 cancers in males and 1.3% of the total cancers in females were laryngeal cancers. They were usually located in the supraglottic or glottic region and the larynx was the least common cancer site except for the pharynx and nasopharynx. Since 1950, the annual death rate for cancer of the larynx has remained unchanged at 2 per 100,000 population for males and .02 per 100,000 population for females. Death rates for laryngeal cancer increased dramatically in males over 50 years of age. Data from a cancer registry in Papua, New Guinea reveal that, in the period 1958-1970, laryngeal cancers accounted for 2.3% of a total of 2,479 cancers in males and 0.8% of a total of 1,643 cancers in females. Of the total of 40 cancers reported, 20 were in the supraglottic or glottic region and 16 were too large to locate precisely. Peak incidence was in males aged 50-60 years. Possible etiological factors in the development of laryngeal cancer such as cigarette smoking, alcohol consumption, and continuous irritation are discussed.

- 7116 EPIDEMIOLOGICAL ASPECTS ON LARYNGEAL CARCINOMA IN SCANDINAVIA. (Eng.) Martensson, B. (Dept. Otolaryngology, Karolinska Sjukhuset, Stockholm, Sweden). *Laryngoscope* 85(7):1185-1189; 1975.

A comparison of the incidence of cancer of the larynx per 100,000 male population of Finland, Iceland, Norway and Sweden reveals the frequency of occurrence in Finland is 3.5 that of the other Scandinavian countries. The difference occurs because of the higher incidence of laryngeal carcinomas of the supraglottic region in Finland since incidence of glottic region carcinomas is similar. Laryngeal carcinomas are more likely to occur at a younger age in Finland (50-59 years) whereas age distribution in Sweden and Norway is the same. Incidence is much higher in Finland for primary carcinomas of the bronchus and lung but not for carcinomas of the digestive organs, oral cavity or pharynx. In the female populations of the Scandinavian countries, incidence rates for all laryngeal carcinomas are

similar. The urban population of these countries is more likely to develop laryngeal cancer than the rural. Studies of smoking habits show a lower proportion of the population smokes in Finland than in Norway, but consumes many more cigarettes.

- 7117 MORBIDITY DUE TO MALIGNANT NEOPLASIAS IN THE USSR. (Rus.) Tserkovnyi, G. F. (No affiliation given); Napalkov, N. P.; Berezkin, D. P.; Preobrazhenskaia, M. N.; Shabashova, N. I.; Mirotvortseva, K. S. *Vopr. Onkol.* 21(1):3-16; 1975.

Statistical data on morbidity due to malignant neoplasias in the USSR during the 1962-1973 period are presented. The overall morbidity rate (per 100,000 inhabitants) was 147.2 in 1962, 172 in 1967, 183.9 in 1972, and 187.7 in 1973. The steady increase in the morbidity rate is presumed to be due to better and more extensive diagnosis and to an increase in the average age of the entire population. The morbidity was lowest in the Tadzhik SSR, Uzbek SSR and Turkmen SSR, and highest in the Estonian SSR, Latvian SSR, and Lithuanian SSR. According to localization of the malignant neoplasia, tumors of the buccal cavity accounted for 1.2/100,000, the lower lip for 3.1, the esophagus for 3.7, the stomach for 22.3, the rectum for 3.1, the larynx for 1.7, the breast for 6.2, the trachea, bronchi and lungs for 12.5, the uterine cervix for 7, the skin for 11.2, the lymphatic and hemopoietic system for 4.4, and other organs for 23.6 in 1973. Similar relations were also established for earlier years. A tendency toward reducing morbidity due to gastric cancer and cancer of the uterine cervix, and increase in the incidence of breast cancer are manifest. The morbidity is distinctly higher among men than among women. The morbidity shows a definite increase with advancing age, starting at 40 yr of age in women, and at 60 yr of age in men.

- 7118 TRENDS IN CANCER INCIDENCE--FACTS OR FALLACY. STUDIES IN FINLAND. (Eng.) Saxen, E. (Finnish Cancer Registry, Helsinki, Finland); Hakama, M. *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 168-174.

Trend figures for cancer incidence in Finland are presented and the situation is forecast for 1980; some of the factors that may affect these figures are discussed. The trends are based upon the incidence data in the Finnish Cancer Registry for 1957-1970. The total cancer incidence has remained approximately unchanged during the study period. A decreasing trend is observable in cancer of the stomach, esophagus, mouth, pharynx, lip and uterine cervix and an increasing trend in the incidence of cancer of the lung in males, cancer of the colon, rectum, pancreas, urinary organs, skin, and malignant lymphomas. If the observed increasing trend continues, it is forecast that in 1980 lung cancer will constitute more than 1/3 of all new cancer

cases in males. The most marked decreasing trend is that of stomach cancer; in 1980, it is expected to constitute no more than 6.4% of malignant tumors. It is also forecast that breast cancer will be the commonest type of cancer in females in 1980, amounting to 1/5 of all new cancer cases. Two factors that may affect the evaluation of trend curves are changes in the definition of cancer and improvements in diagnosis. One effect of changes in the definition of cancer is illustrated by the term carcinoma *in situ*. If these tumors are recorded as cancer, a rising trend in cervical cancer would become observable. Similarly, if cases of carcinoma *in situ* with "buds" and early invasive "occult" carcinomas are grouped under a joint heading of microinvasive carcinoma, a definite decreasing trend of invasive carcinoma might disappear. Improvement in diagnosis, the increase in operations, cases subjected to autopsy, and cases examined microscopically affect the number of recorded cases of malignant tumors. It is concluded that even if the limitations and errors inherent in the evaluation of cancer incidence data are great, many highly illustrative and valuable results have been and will continue to be obtained by the application of epidemiological methods.

- 7119 THE JAPAN-HAWAII CANCER STUDY: A PROGRESS REPORT. (Eng.) Nomura, A. (Kua-kini Hosp., 347 North Kuakini St., Honolulu, Hawaii 96817); Stemmermann, G. N.; Rhoads, G. G.; Glober, G. A. *Hawaii Med. J.* 34(9):309-316; 1975.

The Japan-Hawaii cancer study is following 6,800 Japanese-Hawaiian men born from 1900 through 1919 and comparing the cancer incidence, medical history, and laboratory studies of these men with those of indigenous Japanese in an attempt to isolate specific environmental, biochemical, and pathological variables that may be etiologically associated with different types of cancer. Medical history, particularly with respect to the gastrointestinal tract, was recorded. Most of the subjects took the Hemocult slide test for the early detection of bowel cancer; 4 of 25 subjects with intestinal pathology had asymptomatic cancers. Preliminary analysis of serum from Hawaiian and indigenous Japanese indicated that the prevalence of hepatitis antigenemia in the Japanese-Hawaiians (10/539, 1.85%) does not account for their higher incidence of hepatoma. Sub-populations of the Hawaiian group were subjected to various tests, and the results were compared with those for other groups. A comparison of bowel transit time was made between 63 Japanese-Hawaiian men and 23 Caucasian men; the mean bowel transit time for the Japanese-Hawaiians was 30.8 hr, and for the Caucasians 53.8 hr. Feces from 18 Japanese-Hawaiian men with adenomatous polyps and from 28 normal study men were analyzed for neutral steroids. It was postulated that polyp patients, who are considered to be at greater risk for large bowel cancer than normal individuals, would have more extensive conversion of fecal neutral steroids. The results suggest the opposite; the polyp patients had less conversion of their neutral steroids (36.75 and 69.4% conversion of cholesterol by polyp cases and controls, respectively)

than the controls. A comparative study of 407 gastric cancer cases in Japan and 256 Japanese cases in Hawaii indicated that the estimated incidence rates for diffuse carcinomas were the same in both localities; but the corresponding rates for intestinal, mixed, and other types were substantially lower in Hawaii. These results suggest that the intestinal type is related to environmental factors, and the diffuse type is related to host-related factors. Specimens of large intestine from 202 Japanese-Hawaiian necropsy subjects were compared with 480 autopsy specimens from Japan to identify various types of colonic neoplasms. The results indicate that diverticula and adenomatous and hyperplastic polyps are more prevalent in the Japanese-Hawaiians than in the cases from Japan. Hyperplasia of mammary duct epithelia and apocrine metaplasia were more common in Japanese women in Hawaii than in Japan. As sufficient number of cancer cases develop among the study participants, the relationship of these cancers to potential risk factors identified in the study design can be determined.

- 7120 HISTOLOGICAL VARIATIONS OF TUMOURS IN DIFFERENT COUNTRIES OF AFRICA. (Eng.) Templeton, A. C. (Univ. Minnesota Medical Sch., Minneapolis, Minn.). *Proc. Int. Cancer Congr.* 11th. Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 207-210.

Histological variations of tumors in different countries of Africa were determined and compared to series from other geographical regions. In African patients, about 50% of salivary tumors occur in the parotid and about 50% are benign. Studies in different tribes in Uganda, where the incidence of gastric tumors varies widely, confirm previously published conclusions that the higher the incidence of tumors of the stomach, the higher the proportion of intestinal types of tumor. The site at which colonic tumors arise also varies with the overall incidence. In all African countries, colloid or mucus secreting carcinomas appear more frequently than in European series. Tumors of the nose and sinuses appear relatively frequently in many African countries. Nasopharyngeal tumors are almost exclusively the poorly differentiated lymphoepitheliomatous type throughout Africa. In Uganda, 11 of 41 bronchial cancers were adenocarcinomas; all other tumor types have been seen but the incidence is markedly lower than elsewhere. Breast cancer and tumors of the cervix show no great histological differences in Africa. In the ovary, malignant teratomas and granulosa cell tumors appear to be more common in African subjects. African patients have been shown to have a different pattern of estrogen production than Caucasians which may account for the differences in the incidence of ovarian and testicular tumors between African and Caucasian populations. African series of Wilm's tumor tend to demonstrate a preponderance of the more poorly differentiated types. Tumors of the bladder show striking histological variations in different parts of Africa. In

Uganda, bladder cancer is common and over half the tumors are of squamous type, 20% adenocarcinomas, and 15% transitional. Egyptian series show an even greater predominance of squamous tumors but in all countries transitional cell tumors are relatively unusual. Tryptophan metabolites are often cited as bladder carcinogens and it is suggested that there may be racial variations in mechanisms of handling these products. Tumors of the thyroid show a preponderance of the acinar or follicular type in Africa. Tumors of the jaw appear to be relatively frequent; ameloblastoma is seen regularly. Some African series have shown an excess of the granular cell variant while others do not. Burkitt's lymphoma accounts for a large proportion of lymphoreticular neoplasms in the central lower lying areas of Africa. In Hodgkin's disease in Africa, there is a deficiency of the lymphocyte predominant and the nodular sclerosing type when compared with European and U.S. series which may result from delayed diagnosis in the case of nodular lymphocytic lymphoma.

- 7121 RECORD LINKAGE SYSTEM (WITH SPECIAL REFERENCE TO EPIDEMIOLOGY OF CANCER). (Eng.) Adelman, A. M. (Office of Population Censuses and Surveys, Medical Div., London, U.K.). *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 40-43.

A study of deaths occurring in a sample of 1,528 alcoholics between 1964 and 1973 is presented as an example of the use of data available from routine records of patients registered in the British National Health Service. As expected, the rate of mortality among alcoholics proved to be higher than among the general population; 376 deaths as compared with 131 expected. Excess deaths due to cancer were confined to those persons dying between the ages of 40 and 60 yr of age (45 deaths as compared with 23 expected), with increases distributed mainly among the following sites: buccal cavity and pharynx, digestive organs, respiratory system, breast (in women), and genito-urinary system. A comparison of the mortality rates due to cancer of the upper digestive tract between alcoholics and nonalcoholics, indicates a smaller relative danger to alcoholics in England than observed in Norway and the U.S.A. The study demonstrates the potential of linked records to examine all the available results of particular hazards, in contrast to the usual retrospective type of study in which only one disease is usually examined.

- 7122 CANCER MORTALITY IN FRANCE: NEW ASPECTS OF PRESENTATION AND ANALYSIS OF THE DATA. (Fre.) Berlie, J. (Division de la Recherche médico-sociale de l'INSERM, 44, chemin de Ronde,

Le Vésinet, 78110 France); Laurent, F.; Rezvani, A.; Pen, Y.; Brunet, M. *Bull. Cancer (Paris)* 62(2):161-164; 1975.

The mortality rates for cancer of specific body sites were determined by statistical analysis of data collected from 22 regions of France. In addition, the differences between local rates and national mortality levels were analyzed. The raw data was obtained from death certificates collected since 1968 by a central bureau. Standardization of age differences was achieved by the use of three populations of reference: 1) French population--1968 census, 2) European population, and 3) world population. Graphic representation of the corrected data revealed significant correlations between death from: 1) lung cancer and cancer of the bladder; 2) cancer of the esophagus, stomach and the entire digestive tract, and 3) cancer of various sites in the female reproductive organs. Only two regions had cancer mortality rates for all sites approaching those of national levels. Thus these regions would be most likely to be chosen for morbidity studies. The statistical method utilized can be applied to morbidity studies and to smaller geographical units. The final aim of such studies is the correlation of cancer mortality or morbidity and various factors, i.e., geographic, air pollutants, or smoking, that may be contributory.

- 7123 TRENDS IN CANCER SURVIVAL AMONG U.S. WHITE CHILDREN, 1955-1971. (Eng.) Myers, M. H. (C518 Landow Bldg., Natl. Cancer Inst., Bethesda, Md. 20014); Heise, H. W.; Li, F. P.; Miller, R. W. *J. Pediatr.* 87(5):815-818; 1975.

The National Cancer Institute compiled information on survival rates of 8,282 children under 15 yr of age diagnosed as having cancer between the years 1955 and 1969. The information was gathered from data collected by the End Results Group from the same hospitals, 45% of which were university medical centers. Five-yr survival rates increased from the time period 1955 to 1959 to the time period 1965 to 1969 for cases of leukemia (1 to 5%, respectively), tumors of the brain and nervous system other than neuroblastoma (34 to 45%), retinoblastoma (83 to 91%), Wilms' tumor (41 to 60%), and Hodgkin's disease (42 to 66%). There was little progress in survival during the same time periods for cases of bone sarcoma, soft tissue sarcoma, lymphoma other than Hodgkin's disease, and neuroblastoma.

- 7124 LONG-TERM WORLDWIDE EFFECTS OF MULTIPLE NUCLEAR-WEAPONS DETONATIONS. (Eng.) Anonymous. *Natl. Acad. Sci. Natl. Acad. Eng. Natl. Res. Coun. News Rep.* 25(6):9-12; 1975.

The findings of the National Research Council's Committee to Study the Long-Term Worldwide Effects of Multiple Nuclear-Weapons Detonations (10,000 megatons of TNT equivalent) are summarized. Pre-

dictions relevant to cancer research are: an increase in UV radiation (because of ozone depletion caused by the production of nitric oxide) would probably lead to increased incidence of malignant skin tumors in humans (3-30%) and white-coated animals; an increase in total dose of radioactivity of 4 rem over 30 yr would lead to an increase of about 2% in the spontaneous cancer death rate; the incidence of significant genetic disease would increase from 0.2 to 2% in the first generation with about 4/5ths of the effects occurring in succeeding generations.

- 7125 NEOPLASMS IN PERSONS TREATED WITH X-RAYS IN INFANCY: FOURTH SURVEY IN 20 YEARS. (Eng.) Hempelmann, L. H. (Univ. Rochester Sch. Medicine Dentistry, Rochester, N.Y. 14642); Hall, W. J.; Phillips, M.; Cooper, R. A.; Ames, W. R. *J. Natl. Cancer Inst.* 55(3):519-530; 1975.

The incidence of neoplastic disease was determined by a mail survey of 2,872 young adults given x-ray treatments in infancy and of their 5,005 nonirradiated siblings. The irradiated subjects had more than twice as many malignant and benign tumors as the larger group of nonirradiated siblings. The analysis of data concerning radiation-induced thyroid neoplasms gave information on the effects on tumor induction according to age, sex, and dose. The incidence of cancer in all irradiated females was 2.3 times that in males, and in 15- to 29-yr old women, the incidence was five times that of the rest of the irradiated population. The curve for incidence of thyroid cancer increased with age for both males and females. The incidence of thyroid cancer increased with almost every dose increment, and the incidence of benign tumors was more erratic but still had an upward trend. The data on observed and expected deaths does not indicate any excessive increase in the death rate of either the irradiated population or the sibling population.

- 7126 RADIATION PROTECTION NUCLEAR POWER PLANT PERSONNEL. (Ger.) Albrecht, L. (Staatliches Amt für Atomsicherheit und Strahlenschutz, Berlin); Kruger, F. W. *Technik* 30(8):511-514; 1975.

Radiation protection of nuclear power plant personnel is described. Direct radiation hazards and the release of radioactive gases and liquids are minimized by tight encapsulation of the active installations. Special protective clothing is provided for the power plant personnel who are required to carry personal film dosimeters for evaluation at regular intervals, as well as radiation indicators and alarm devices during special operations. The evaluation of 15,689 dosimeter films used up during the first three years of the operation of the nuclear power plant Rheinsberg showed radiation above the detection limit on 1,381 films (8.8%). The exposure was usually well below

the maximum allowable limit of 5 rem/yr. The limit was exceeded in two extraordinary cases without any serious danger for the persons affected. The inner radiation load is below 1.5 rem/yr.

- 7127 SMEGMA PRAEPUTII AS CARCINOGENIC FACTOR. (Ger.) Stambolovic, B. (Poliklinik für Frauenkrankheiten mit Entbindungsanstalt Lazarevac/Jugoslawien). *Fortschr. Med.* 93(4):174-175; 1975.

Women from different ethnic groups and socioeconomic levels in Yugoslavia were investigated for a relationship between the incidence of cervical carcinoma and smegma praeputii; and the importance of sexual hygiene in the male is emphasized due to a possible etiologic relationship between smegma infection and cancer in either of the sexual partners. Neither tumors of the cervix, nor precancerous states were found among 504 women living in a rural area, while two cases of carcinoma of the cervix were diagnosed among 1,297 Muslim women living in an urban area. One case was found among 487 rural women, and ten cases were diagnosed among 2,064 urbanized Christian women. Six cases were found among 500 women belonging to a low socioeconomic stratum, in which inadequate genital hygiene may prevail among the non-circumcised husbands. The epidemiological findings indicate that conditions leading to poor sexual hygiene are likely to increase the incidence of smegma infection and of subsequent carcinomas of the penis and/or cervix. Such preventive measures as health education programs and circumcision of newborn males are suggested.

- 7128 N-NITROSODIMETHYLAMINE IN COLD-SMOKED SABLEFISH. (Eng.) Gadbois, D. F. (Natl. Marine Fisheries Service, Northeast Utilization Res. Center, Gloucester, Mass. 01930); Ravesi, E. M.; Lundstrom, R. C.; Maney, R. S. *J. Agric. Food Chem.* 23(4):665-668; 1975.

Cold smoked sablefish treated with brine solutions containing 0 to 1300 ppm of sodium nitrite were analyzed for N-nitrosodimethylamine (DMNA). Samples of the fish were subjected to gas-liquid chromatography immediately after processing and again after two weeks storage at 40 Fahrenheit. Trace amounts of DMNA (less than 10 ppb) were detected in samples with nitrite levels of 0 to 550 ppm. Storage at 40 Fahrenheit for two weeks decreased the DMNA slightly. An automated GC-MS system was used to confirm the identity of DMNA. Samples containing more than 500 ppm of sodium nitrite were analyzed on the GC-MS by pooling eight samples of eluents from silica gel columns. Prior to the column chromatography on the silica gel, the samples had been digested in methanolic potassium hydroxide, subjected to liquid-liquid extraction with methylene chloride, and the nitrosamines distilled from alkaline solutions. The combined sample was further concentrated before injection on the GC-MS column. Even when nitrite levels in the fish were as high as 550 ppm, the only nitrosamine found was DMNA in concentrations of less than 10 ppm.

- 7129 METHODS FOR ASSAY OF AFLATOXINS IN COCONUT PRODUCTS. (Eng.) Samarajeewa, U. (Dept. Bacteriology, Univ. Sri Lanka, Peradeniya, Sri Lanka); Arseculeratne, S. N. *J. Food Sci. Technol.* 12(1):27-31; 1975.

Several analytical procedures, established for assay of aflatoxin in peanuts, are studied for their applicability to coconut products. The different forms of coconut subjected to assay were: (1) grated fresh coconut; (2) residues left after mechanical or solvent extraction of oil from fresh coconut; (3) naturally contaminated samples of copra meal collected from mills; (4) rehydrated copra meal inoculated with *Aspergillus parasiticus*. The solvent systems used were aqueous acetone, chloroform-water, or hexane-aqueous methanol. Methods for treatment of the solvent systems and the coconut sample included shaking with glass beads in wrist action shaker for periods of 1/2 hour to four hours, homogenization at high speed for three minutes, Soxhlet extraction for four hours with a siphon rate of 10-12 cycles/hour. All estimations were performed on silica gel TLC plates using long wave UV light. Also, chromatograms were developed in two solvent systems. All methods studied gave similar values for aflatoxin content of the samples. The procedure utilizing extraction in 70% aqueous acetone with three homogenizations on residue and lead acetate purification is considered the best method for routine analysis of solid coconut products. It is applicable to samples with at least 0.01 ppm aflatoxin. The use of a single homogenization, extracting about 74% of the aflatoxin and a correction factor is recommended for rapid assay of commercial coconut products.

- 7130 MULTIPLE INTERACTION EFFECTS OF CIGARETTE SMOKING. EXTRAPULMONARY CANCER. (Eng.)

Hammond, E. C. (Mount Sinai Sch. Medicine, City Univ. New York, N.Y.); Selikoff, I. J.; Seidman, H. *Proc. Int. Cancer Congr. 11th.* Vol. 3 (*Cancer Epidemiology, Environmental Factors*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 147-150.

The results of two studies concerning the incidence of cancer, one among smokers and one among asbestos workers, were compared. Over one million adults over the age of 30 were questioned about their smoking habits (and other factors) and then traced from 1959 to 1965. In another study, a large percentage of 17,800 asbestos workers responded to questions on smoking habits and other factors; a total of 102,864 man-yr of experience were covered in this study. The highest mortality ratios were, with one exception (bladder cancer), for cancer of sites (lung, buccal cavity, pharynx, larynx, and esophagus) directly exposed to cigarette smoke or material condensed from cigarette smoke. For asbestos workers, high mortality ratios were found in cancer of sites most directly exposed to inhaled asbestos dust (the same sites most directly exposed to cigarette smoke). Also, many deaths

occurred from pleural and peritoneal mesothelioma. The asbestos workers had increased death rates for cancer of all other sites combined. When the expected and observed number of cancer deaths in asbestos workers were broken down by smoking habits, results were similar to those seen in the general population of smokers and nonsmokers. Cigarette smoking without exposure to asbestos dust was associated with increased death rates from cancer of certain sites. Among smokers, the ratio of mortality from lung cancer was nearly four times higher among asbestos workers than among nonsbestos workers. Among nonsmokers, mortality figures for asbestos workers and nonsbestos workers were similar. The authors conclude that exposure to asbestos dust greatly increases the incidence of lung cancer among cigarette smokers but not among nonsmokers.

- 7131 PARTICULATE LEAD CONCENTRATIONS IN MELBOURNE AIR. (Eng.) Fisher, A. (Environment Protection Authority, State Government of Victoria, Australia); LeRoy, P. *Clean Air (Heidelberg, Aust.)* 9(3):56-57; 1975.

Particulate lead concentration in the air was determined at a site near the Melbourne (Australia) business district to see if diurnal variations could be attributed to the effects of automobile exhaust emissions. Seventy-two samples were collected (over 12 days) 1.5 meters above ground level on cellulose acetate filters. Analysis with an atomic absorption spectrophotometer revealed that the diurnal variation had a pattern similar to that of the automobile population; particulate lead concentrations were higher in the morning and in the afternoon.

- 7132 LUNG CANCER AMONG COKE OVEN WORKERS. A REPORT TO LABOUR STANDARD BUREAU, MINISTRY OF LABOUR, JAPAN. (Eng.) Sakabe, H. (No affiliation given); Tsuchiya, K.; Takekura, N.; Nomura, S.; Koshi, S.; Takemoto, K.; Matsushita, H.; Matsuo, Y. *Ind. Health* 13(1/2):57-68; 1975.

An epidemiological study on the lung cancer incidence among Japanese coke oven workers was undertaken. Data were collected via questionnaires completed by industrial physicians or chief inspectors. Among the 36 firms operating coke ovens, there was no significant difference in the incidence of malignant neoplasia of any site between retired coke oven workers of the iron and gas industries and Japanese men in general. However, eight deaths due to lung cancer occurred in the retired coke oven workers of the iron and steel industries, as compared to an expected incidence of 3.38 ($p \leq 0.022$). While the observed frequency of lung cancer (16.5%) in malignant neoplasia of all sites among any of the workers showed no significant difference from that expected of the general population, a greater relative frequency of 22.2% was noted in employees of the iron and steel-works ($p \leq 0.05$). Lung cancer occurred after five

yr of working and at the age of over 50 yr among workers of city gas companies, but occurred after 10 yr of working in the affected iron and steel workers. Thus lung cancer onset in the city gas industry showed a shorter working period and longer latent period than in the iron and steel works; reliable information on the smoking habits of the workers was not obtained. A brief literature review notes no lung cancer found in 14,149 person years among present coke oven workers, and no significant differences between the expected and observed number of lung cancer deaths among present and retired coke oven workers. It is suggested that the existence of coal tar and volatiles from coal tar in the coke oven emissions may be at least partially responsible for the high cancer incidence among the coke oven workers in the iron and steel works. Prophylactic recommendations include mechanization, respiratory protective devices, and physical check-ups for coke oven workers.

- 7133 EXPOSURE TO COKE OVEN EMISSIONS--LABOR/OSHA PROPOSES STANDARDS FOR EXPOSURE. (Eng.) Anonymous. *Fed. Regist.* 40(148):32267-32282; 1975.

The Department of Labor (Occupational Safety and Health Administration) outlines proposals for the regulation of exposure to coke oven emissions, which are known to pose a significant risk of cancer to exposed working populations. The proposed standard contains a requirement limiting employee exposure to an 8 hr time-weighted average concentration based on a 40-hr wk of respirable particulates of 0.3 mg/m³. The proposal also provides for employee exposure measurements, methods of compliance, personal protective equipment and clothing, training, medical surveillance, and recordkeeping.

- 7134 TRICHLOROETHYLENE: PROPOSED OCCUPATIONAL EXPOSURE STANDARD. (Eng.) Anonymous. *Fed. Regist.* 40(203):49032-49045; 1975.

The Department of Labor (Occupational Safety and Health Administration) proposes to amend existing regulations governing occupational exposure to trichloroethylene. Ninety percent of the trichloroethylene consumed in the U.S. is used as a solvent in vapor degreasing operations, 5% as a dry-cleaning or extractive solvent, and the remainder as an intermediate in the chemical industry. Preliminary experimentation conducted by the National Cancer Institute has indicated that the substance is carcinogenic in mice, but the Department of Labor does not believe that it is appropriate at this time to treat trichloroethylene as a human carcinogen. The proposed new standard would retain the current 8 hr time-weighted average limit for exposure to airborne concentrations of trichloroethylene of 100 ppm, and reduce the ceiling limit from 200 ppm to 150 ppm. In addition, the acceptable maximum peak of 300 ppm for 5 min in any 2 hr period would be deleted. The proposed standard would also add detailed requirements for measuring employee exposures, methods of compliance, respiratory pro-

tection, hazardous and emergency situations, protective equipment, housekeeping, training, signs and labels, medical surveillance, and recordkeeping.

- 7135 AUTORADIOGRAPHIC STUDY OF THE PARAMETERS OF THE CELLULAR CYCLES OF THE HUMAN TESTICLE TUMOURS IN THE TISSUE CULTURE. (Rus.) Terent'eva, T. G. (All-Union Res. Inst. Antibiot., Moscow, U.S.S.R.); Sokolov, A. B.; Laskina, A. B.; Gibadulin, R. A. *Biull. Eksp. Biol. Med.* 79(4):95-97; 1975.

The parameters of the mitotic cycle of monolayer cultures of human testicular teratoblastoma were studied by autoradiography following incubation with tritiated thymidine. The primary cultures were incubated on the 16th day of growth. The duration of the mitotic cycle was 83.6 hr, and duration of the period of DNA synthesis (S) was 5.35 hr. The duration of the presynthetic period (G₁) was 60.25 hr. The first labeled mitoses were observed six hours after incubation with thymidine, the percentage of labeled mitoses was 66.6% after 24 hr, and 100% after 48 hr. The mitotic index was 0.4-0.5% throughout the experiment.

- 7136 KINETICS OF CELL PROLIFERATION AND CELL LOSS IN THE PERIPHERAL AND CENTRAL PARTS OF WALKER TUMOURS GROWING IN RATS AND NUDE MICE. (Eng.) Broyn, T. (Inst. Pathology, Univ. Oslo, Rikshospitale Oslo, Norway). *Virchows Arch. [Zellpathol.]* 18(3):181-191; 1975.

To investigate whether or not the lower rate of cell proliferation on the peripheral zone rather than in the main tumor mass is caused by local factors, or specific cellular immunity, 51 female Wistar rats and 32 male nude BALB/c mice were injected sc with Walker 256 tumor cells in two experimental series. The animals in the first series were injected ip with ³H-TDR (1000 µCi/kg) 0.5 to 14 hr before sacrifice (6 to 9 days after tumor cell injection). The animals in the second series were injected sc with 3 mg/kg vinblastine sulfate and sacrificed on day 5, 3 hr after tumor cell injection. The cells in the main tumor mass and on the tumor periphery were counted. Cell proliferation on the tumor periphery was considerably lower than in the main tumor mass in both rats and mice. The author concludes that the described growth pattern is probably a general characteristic of the Walker tumor, and that the low rate of proliferation at the periphery is not caused by specific immunological mechanisms.

- 7137 KINETIC ANALYSIS OF CELL SIZE AND DNA CONTENT DISTRIBUTIONS DURING TUMOR CELL PROLIFERATION: EHRLICH ASCITES TUMOR STUDY. (Eng.) Kim, M. (Sch. Electrical Engineering, Cornell Univ., Ithaca, N.Y.); Woo, K. B. *Cell Tissue Kinet.* 8(3):197-218; 1975.

The simultaneous occurrence of several processes in the growth of tumor cell populations was characterized by evaluating the cell age, cell size, and DNA content distributions of Ehrlich

- ascites tumor using a discrete-time kinetic model. For computer simulation, the age of the experimental tumor measured in real time was converted to one expressed in terms of mean generation times elapsed since the transplantation of the tumor. The cell age distribution during the growth period was obtained and used to specify the cell behavior of cell cycle, size, and DNA content distributions by a linear transformation of the state transition matrices. Analysis of the time-course behavior became rapid as the cell population reached 200×10^6 , with the higher rate of cellular DNA synthesis of the mean generation time of proliferating cells with increasing size of the tumor was slow at the beginning of tumor inoculation but became rapid as the cell population reached 200×10^6 , corresponding to a pronounced decrease in the growth rate of tumor. The rate of cell death from the proliferating or non-proliferating population did not change significantly during most of the growth period, indicating that the rates of cell death do not vary with tumor aging. The time-course behavior of cell age distribution showed a large peak at the end of the age distribution with the aging of the tumor due to the accumulation of cells in the G_2 , M phase as confirmed by variations in the cell size distributions of the $G_1 + S$ and $G_2 + M$ phases. The authors concluded that, with the higher rate of cellular DNA synthesis close to the end of the S phase, the model results show the distribution of DNA content with the increase of cells in the $G_2 + M$ phase with aging of the tumor. It is also concluded that the process of transition of proliferating cells to the resting states depends on the population size of the tumor. The latter in turn depends on the change in the growth medium and the increase in some type of growth inhibitor brought about by the increasing size of the tumor.
- 7138 INCIDENCE OF BREAST CANCER. (Eng.) Lee, J. A. H. (Dept. Epidemiology and International Health, Univ. Washington, Seattle, Wash. 98195); Weatherall, A. F. *Lancet* 2(7937):713; 1975.
- 7139 BREAST CANCER IN YOUNG WOMEN. (Eng.) Waterhouse, J. A. H. (Queen Elizabeth Hosp., Birmingham, England); Prior, M. P. *Br. Med. J.* 3(5980):434; 1975.
- 7140 A NOTE ON THE SELECTION OF SWINE RATION INGREDIENTS WITH AN AFLATOXIN CONTAMINATION LEVEL BELOW $1 \mu\text{G/KG}$. (Eng.) Ambrecht, B. H. (Bureau Veterinary Medicine, Food and Drug Administration, Rockville, Md. 20852); Jacobson, W. C.; Wiseman, H. G. *Bull. Environ. Contam. Toxicol.* 14(4):401-403; 1975.
- 7141 AFLATOXIN CONTAMINATION OF CORN IN THE FIELD. (Eng.) Anderson, H. W. (The Quaker Oats Company, John Stuart Laboratories, Barrington, Ill. 60010); Nehring, E. W.; Wichser, W. R. *J. Agric. Food Chem.* 23(4):775-782; 1975.
- 7142 SAMPLING COTTONSEED LOTS FOR AFLATOXIN CONTAMINATION. (Eng.) Velasco, J. (Agricultural Marketing Res. Inst., Beltsville, Md. 20705); Whitaker, T. B. *J. Am. Oil Chem. Soc.* 52(6):191-195; 1975.
- 7143 OCCUPATIONAL CANCER IN SKIN CARCINOGENESIS. (Eng.) Everall, J. (Skin Dept., Royal Ardsen Hosp., London, U.K.). *Proc. Int. Cancer Congr. 11th. Vol. 3 (Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26; 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 91-93.
- 7144 LYMPHORETICULAR MALIGNANCIES: EPIDEMIOLOGIC AND RELATED ASPECTS. (Eng.) Vianna, N. J. (Cancer Control Bureau, New York State Dept. of Health, Albany, N.Y.). Lancaster, England, Medical and Technical Publishing, 1975, 136 pp.
- 7145 HEPATOCYTIC CARCINOMA IN CATTLE AND ITS RELATION TO BILIARY CIRRHOSIS OF FASCIOLOLARIOSIS. (Ger.) Vitovec, J. (Statni veterinarni ustav, Tr. Obr. miru 79, 37139 Ceske Budejovice, Czechoslovakia). *Vet. Pathol.* 11(6):548-557; 1974.
- 7146 HODGKIN'S DISEASE: AN EPIDEMIOLOGICAL STUDY COVERING 140 CHILDREN--URBAN/RURAL RATIO, OCCUPATION OF PARENTS, CONTACTS WITH PETS AND DOMESTIC ANIMALS. (Ger.) Dorken, H. (Univ.-Krankenhaus Eppendorf, I. Med. Klinik, BRD - 2 Hamburg 20, Martinistr. 52, West Germany). *Arch. Geschwulstforsch.* 45(3):283-298; 1975.
- 7147 RECOVERY OF HeLa CELLS FROM INHIBITED ENTRY INTO MITOSIS INDUCED BY *p*-FLUOROPHENYL-ALANINE. (Eng.) Wheatley, D. N. (Medical Sch., Univ. Aberdeen, Aberdeen AB9 2ZD, Scotland); Henderson, J. Y. *Exp. Cell Res.* 92(1):211-220; 1975.
- 7148 A SPATIAL AND TEMPORAL ANALYSIS OF FOUR CANCERS IN AFRICAN GOLD MINERS FROM SOUTHERN AFRICA. (Eng.) Harington, J. S. (Cancer Res. Unit of Natl. Cancer Assoc. of South Africa, P.O. Box 1038 Johannesburg, South Africa); McGlashan, N. D.; Bradshaw, E.; Geddes, E. W.; Purves, L. R. *Br. J. Cancer* 31(6):665-678; 1975.
- 7149 LYMPHOGANULOMATOSIS INCIDENCE. (Rus.) Plotnikov, Iu. K. (D. I. Ul'yanov Kuybyshev Medical Inst., Kuybyshev, U.S.S.R.); Sukhov, V. M.; Kharkova, E. N. *Klin. Med. (Mosk.)* 53(3):90-94; 1975.

7150 STUDY OF THE EFFECT OF AIR POLLUTION ON
 LUNG CANCER AND INTESTINAL CANCER MORTALITY
IN MONTREAL ISLAND DURING THE 1963-1966 PERIOD.
(Fre.) Lavergne, B. (Institut de microbiologie et
d'hygiene de Montreal, Canada); Frappier-Davignon,
L.; St-Pierre, J. *Union Med. Can.* 104(8):1397-1406;
1975.

See also:

- * (Rev): 6601, 6602, 6609, 6628, 6633, 6643,
 6644, 6645, 6647, 6653, 6654, 6657,
 6663
- * (Chem): 6692, 6708, 6783, 6792
- * (Phys): 6809, 6815, 6816
- * (Viral): 6850
- * (Epid-Biom): 7017

MISCELLANEOUS

7151 ACTH AND PROSTAGLANDIN RECEPTORS IN HUMAN ADRENOCORTICAL TUMORS: APPARENT MODIFICATION OF A SPECIFIC COMPONENT OF THE ACTH-BINDING SITE. (Eng.) Saez, J. M. (Unite de Recherches Endocriniennes et Metaboliques chez l'Enfant. I.N. S.E.R.M., Hopital Debrousse, 69322 Lyon Cedex 1, France); Dazord, A.; Gallet, D. *J. Clin. Invest.* 56(3):536-547; 1975.

The failure of certain adrenal tumors to respond to ACTH was investigated *in vivo* by administration of corticotropin-(1-24)-tetracosapeptide (ACTH₁₋₂₄) and dexamethasone and *in vitro* by studying the binding properties of ACTH₁₋₂₄ and prostaglandin E₁ (PGE₁) and their effect on adenylate cyclase activity of the tumors' crude membranes. In five cases, the stimulation of cortisol production in isolated adrenal cells by both hormones and dibutyryl cyclic AMP (cAMP) was also studied. The results obtained in 13 hormone-producing tumors of the human adrenal cortex (ten carcinomas and three adenomas) were compared with those found in normal human adrenal glands. According to the adenylate cyclase responses to ACTH₁₋₂₄ and PGE₁, the tumors fell into different categories. In the first group were six tumors in which the adenylate cyclase was stimulated by both ACTH₁₋₂₄ and PGE₁; in addition, specific binding could be demonstrated for the two hormones in all six. The binding affinity for ¹²⁵I-ACTH₁₋₂₄ was found to be about ten times higher than that for corticotropin-(11-24)-tetradecapeptide (¹²⁵I-ACTH₁₁₋₂₄). In the one tumor in which the experiment was performed, bound ¹²⁵I-ACTH₁₋₂₄ was displaced by corticotropin-(1-10)-decapeptide (¹²⁵I-ACTH₁₋₁₀). These results were similar to the ones found in normal human adrenal preparations. A second group encompassed six tumors in which the steroidogenesis *in vivo* and the adenylate cyclase activity were insensitive to ACTH₁₋₂₄ but in which the enzyme was stimulated by PGE₁ and NaF. However, these preparations bound ¹²⁵I-ACTH₁₋₂₄ and ¹²⁵I-ACTH₁₁₋₂₄, the binding affinity being similar for both peptides but ten times lower than the one found in normal adrenal cortex for ¹²⁵I-ACTH₁₋₂₄. In the only case of this group where it was tested, ACTH₁₋₁₀ did not displace bound ¹²⁵I-ACTH₁₋₂₄. This result strongly suggests the possibility of a modification or a loss of the receptor site that binds the N-terminal sequence (1-10) of ACTH, the biologically active part of the molecule. In the last tumor, both PGE₁ and ACTH were unable to stimulate adenylate cyclase activity and steroid production in a preparation of isolated adrenal cells, although steroidogenesis was stimulated by cAMP. No specific binding for PGE₁ could be demonstrated. However, ¹²⁵I-ACTH₁₋₂₄ and ¹²⁵I-ACTH₁₁₋₂₄ were found to be bound to the tumor with the same affinity.

7152 INITIATION OF CELL PROLIFERATION IN CULTURED MOUSE FIBROBLASTS BY PROSTAGLANDIN F_{2α}. (Eng.) De Asua, L. J. (Imperial Cancer Res. Fund, P. O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England); Clingan, D.; Rudland, P. S. *Proc. Natl. Acad. Sci. USA* 72(7):2724-2728; 1975.

The ability of a series of structurally related prostaglandins (PGs) to initiate DNA synthesis and cell division in quiescent Swiss mouse 3T3 cells was studied. The prostaglandins were added after newly plated cells became quiescent and the cells were labeled with [methyl-³H]thymidine (3 μCi/ml) 6-28 hr after the addition of the PGs. DNA synthesis and the percentage of radioactively labeled nuclei were calculated thereafter, as were the intracellular levels of cyclic AMP and cyclic Aguanosine monophosphate. Prostaglandin F_{2α} (PGF_{2α} 75-400 ng/ml) increased the number of cells in the 3T3 cultures by 40-50% within 72 hr, the number of cells obtained being dependent on the PG concentration. Although insulin (50 ng/ml) alone produced little or no increase in cell number, when added with PGF_{2α} it increased the number of new cells at 72 hr to a factor of 2-fold over that observed with PG alone. PGF_{2α} greatly decreased the amount of serum required to form a confluent monolayer of 3T3 cells, and the increase in final cell density caused by the PG became progressively smaller with higher serum concentrations. The addition of PGF_{2α} to simian virus 40 (SV40)-transformed 3T3 cells produced no increase in cell number. PGF_{2α} at 200 ng/ml greatly stimulated the incorporation of [³H]thymidine into cellular DNA. Prostaglandin E₁ (PGE₁) and prostaglandin E₂ were less effective than PGF_{2α} in this respect, and PGB₁ was totally ineffective. Again, insulin greatly enhanced the effect of PGF_{2α}, and a synergistic effect between PGF_{2α} and low serum concentrations (1%) was observed. The proportion of cells synthesizing DNA was decreased 50% and 10% by the addition of PGE₁ and PGF₂ (50 μg/ml), respectively, 20 min before the addition of 10% serum. Arachidonic acid, linoleic acid, eledoisin, phsalaemin, carbamyl choline, acetylcholine, and oxytocin did not appreciably stimulate DNA synthesis in 3T3 cells. Polyphoretin phosphate reduced by 60% the ability of PGF_{2α} to initiate DNA synthesis. PGF_{2α} (300 ng/ml) increased the intracellular cyclic GMP levels 5-fold and slightly decreased the cyclic AMP concentrations; insulin potentiated this effect. The data show that PGs can act as positive or negative extracellular regulators of cell growth, and that these effects can be correlated with changes in the intracellular cyclic nucleotide levels.

7153 INTERACTION OF F1 HISTONE WITH SUPERHELICAL DNA. (Eng.) Vogel, T. (Lab. of Biochemistry, Natl. Cancer Inst., Bethesda, Md. 20014); Singer, M. F. *Proc. Natl. Acad. Sci. USA* 72(7):2597-2600, 1975.

The superhelicity of double-stranded, closed circular Simian virus 40 (SV40) component I DNA was altered by the addition of various amounts of ethidium bromide, and the interaction of f1 histone with the resulting series of molecules of various superhelicities was studied. DNA and histone were incubated in a total volume of 0.1 ml containing 0.05 M Tris-HCl (pH 7.8), 0.1 M NaCl, and 1 mM EDTA. After various incubation periods at 23 C, reaction mixtures were passed through Millipore filters. The radioactivity on the filters was measured after drying. When ¹⁴C-labeled SV40 component I DNA was allowed

to react with fl histone and various amounts of unlabeled DNA were subsequently added, the amount of radioactive DNA detected in the complex decreased after filtration. The same results were obtained when the labeled and unlabeled DNA were mixed prior to the addition of histone, indicating that the interaction between fl histone and superhelical DNA is readily reversible. The extent of interaction of fl histone with superhelical DNA was a direct function of the degree of superhelicity, regardless of whether it was of the positive or negative sense. It appears that the binding of the ethidium to the superhelix does not itself influence the interaction with fl histone but rather the ability of fl to interact with the DNA is altered only by the conformational changes that secondarily accompany the binding of ethidium. The change in the amount of DNA trapped on the filters as a function of superhelix density may reflect changes in the association constant for the fl histone-DNA interaction or in the number of high affinity binding sites on the DNA. This change may also simply reflect an alteration in the DNA structure, changing its ability to pass through the filter. The data also suggest that the interaction of fl histone and superhelical DNA in the presence of ethidium may offer a new and simple method for estimating the superhelical density of closed circular duplex DNAs.

- 7154 DIFFERENTIAL EFFECTS OF ISOLEUCINE DEPRIVATION ON CELL MOTILITY, MEMBRANE TRANSPORT AND DNA SYNTHESIS IN NIL 8 HAMSTER CELLS. (Eng.) Kohn, A. (Israel Inst. for Biological Res., Ness Ziona, Israel). *Exp. Cell Res.* 94(1):15-22; 1975.

Differential effects of isoleucine deprivation on cell motility, membrane transport, and DNA synthesis in NIL 8 hamster cells were studied. The motility of NIL 8 hamster cells was largely independent of DNA synthesis as measured by thymidine incorporation and labeling of the nuclei. The motility of cells arrested in early G 1 by isoleucine deprivation was inhibited by only 30-40% as compared with that of cells in full medium. In contrast, DNA synthesis, ceased completely after 25-30 hr. Uridine and thymidine transport in these cells was not affected by isoleucine starvation, while deoxyglucose uptake was reduced by 30-40%. In contrast, serum deprivation of this cell line caused the arrest of both motility and DNA synthesis (90%). Serum deprivation also reduced the uptake rate of glucose and of thymidine to about 10-15% of that found in serum-stimulated cells. The physiological state of cells arrested in G 1 by lack of isoleucine is thus different from that of cells made quiescent by serum deprivation.

- 7155 INCREASE IN THE ACCUMULATION OF GLOBIN mRNA IN IMMATURE ERYTHROBLASTS IN RESPONSE TO ERYTHROPOIETIN *IN VIVO* OR *IN VITRO*. (Eng.) Conkie, D. (Beatson Inst. Cancer Res., Glasgow, G3 6UD, Scotland); Kleiman, L.; Harrison, P. R.; Paul, J. *Exp. Cell Res.* 93(2):315-324; 1975.

The role of erythropoietin in globin mRNA formation in pro-erythroblasts from mouse livers at various stages of development, mouse fetal liver

cell suspensions cultured *in vitro* with erythropoietin, and adult mouse spleens under anemic conditions (providing elevated erythropoietin levels *in vivo*) was investigated. Globin mRNA was localized by the *in situ* hybridization of highly-labeled DNA transcripts of adult globin mRNA to fixed slide preparations of the cells, followed by autoradiographic detection of the hybrid. About 50% of the erythroid cells in suspensions of total fetal liver cells from Swiss (Porton) mice at 11.5 day of gestation were pro-erythroblasts. Of these, only 2% contained detectable quantities of globin mRNA. After 15.5 day of gestation, the proportion of pro-erythroblasts declined to 11%, of which 36% contained globin mRNA. When cells from fetal livers of 13.5 day gestation time were cultured *in vitro* for 24 hr with human urinary erythropoietin (0.6 U/ml), the pro-erythroblast compartment proliferated and the proportion of the pro-erythroblasts with detectable amounts of globin mRNA increased from about 20% to 85%. In adult mice made anemic by the ip administration of phenylhydrazine (0.1 ml/20 g of 0.8% solution, given at 0 hr, 16 hr, and 24 hr), the spleen increased in size four- to five-fold after 112 hr. The proportion of erythropoietic cells was elevated from 5% to 80% of the total spleen cell population. The percentage of pro-erythroblasts that contained globin mRNA sequences was high (74 to 90%) even during the earliest stages of anemia; more mature erythroblasts progressively came to predominate in the spleen. The authors conclude that erythropoietin supports the proliferation of pro-erythroblasts and enables these cells to accumulate globin mRNA before they differentiate morphologically to produce basophilic erythroblasts.

- 7156 RELATION OF CELL TYPE AND CELL DENSITY TO THE DEGREE OF POST-TRANSCRIPTIONAL MODIFICATION OF tRNA^{Lys} AND tRNA^{Phe}. (Eng.) Katze, J. R. (Univ. Southern California Sch. Medicine, Los Angeles, Calif. 90033). *Biochim. Biophys. Acta* 407(4):392-398; 1975.

Cell density-dependent isoaccepting differences in transfer RNA^{Lys} (tRNA^{Lys}) and tRNA^{Phe} from simian virus 40 (SV40)-transformed BALB/3T3 cells grown to different cell densities, from untransformed BALB/3T3 cells grown to confluency, and from BALB/c mouse liver were compared. SV40-transformed cells were inoculated into roller bottles (1 x 10⁷ cells in 200 ml medium) on day 1, and the medium was changed on days 4, 6, and 8. Cultures were harvested 18-21 hr after medium change. BALB/3T3 cells were inoculated at about 5 x 10⁵ cells per bottle; the medium was changed on days 4 and 7 (at which time they were confluent) and harvested on day 8. The tRNA was isolated, treated with cyanogen bromide, and aminoacylated with all amino acid concentrations at 10 M. Isoaccepting species were separated by reverse-phase chromatography. At least nine tRNA species were resolved. With increasing cell density in culture, the degrees of the peroxy-Y modification in tRNA, and in an undetermined modification in tRNA, became more like that of differentiated tissue (liver). Because precursor/product relationships appeared to exist among the unmodified and modified

forms of the isoaccepting species for each of these tRNAs, it is concluded that these findings support the view that the often reported differences in tRNA isoaccepting spectra result primarily from differences in posttranscriptional modifications, rather than from different tRNA transcripts.

- 7157 N^6, O^2' -DIMETHYLADENOSINE A NOVEL METHYLATED RIBONUCLEOSIDE NEXT TO THE 5' TERMINAL OF ANIMAL CELL AND VIRUS mRNAs. (Eng.) Wei, C.-M. (Natl. Inst. Allergy and Infectious Diseases, Natl. Inst. Health, Bethesda, Md. 20014); Gershowitz, A.; Moss, B. *Nature* 257(5523):251-252; 1975.

A novel nucleoside, designated A*m, found in HeLa cell mRNA was characterized. The 5'-terminal oligonucleotides of HeLa mRNA were digested with P_1 nuclease and nucleotide pyrophosphate to liberate methyl-labeled pA*m. Methyl-labeled pA*m comigrated with pA on paper electrophoresis at pH 3.5, indicating that pA*m is a derivative of adenosine. PA*m was treated with 1 N HCl at 100 C to liberate the free base. About half of the methyl-labeled cochromatographed with N^6 -methyl-adenine (m^6 Ade). HeLa cell mRNA was then labeled with 2,8- 3 H-adenosine and subjected to combined P_1 nuclease and alkaline phosphatase digestion followed by adsorption of the enzyme-resistant material to a DEAE-cellulose column. The 5'-terminal oligo-nucleotide containing A*m was separated from all but a small amount of the adenosine residues. Nucleoside analysis indicated incorporation of radioactive isotope into A*m. The purified 2,8- 3 H-A*m was treated with 1 N HCl and the labeled base released was identified as m^6 Ade in three different chromatographic systems. The sugar moiety of A*m was characterized by cleaving methyl- 3 H-A*m with spleen purine nucleoside phosphorylase in the presence of phosphate. The labeled product cochromatographed with 2'-O-methylribose-1-phosphate derived from authentic Am. It was concluded that the novel nucleoside found in HeLa cell mRNA (and in the mRNA of L cells and adenoviruses) is N^6, O^2' -dimethyladenosine.

- 7158 A LEUKAEMIC CELL MUTANT WITH A THERMOLABILE ALANYL-TRANSFER RNA SYNTHETASE. (Eng.) Sato, K. (Res. Inst. for Microbial Diseases, Osaka Univ., Yamada-kami, Suita 565, Japan). *Nature* 257(5529):813-815; 1975.

A temperature-sensitive mutant of L5178Y murine leukemic cells (*ts3*) with a thermolabile L-alanine-tRNA synthetase was isolated. At a concentration of 10^{-4} M L-alanine, these cells could grow at a nonpermissive temperature (39 C) if provided with hypoxanthine and sodium pyruvate, but above concentrations of 1 mM L-alanine, hypoxanthine and pyruvate were dispensable. No other L-amino acid could be substituted, nor could D- or β -alanine. Cell growth was inhibited at concentrations above 30 mM alanine. To determine if alanine biosynthesis was impaired at high temperatures, cell extracts were assayed before and after heating. The initial specific activities of alanine aminotransferase, expressed as mole pyruvate formed per minute per mg of protein, were 14.0 and 15.2 and the

residual activities after 60 min at 40 C were 11.6 and 12.8 for wild-type and *ts3*, respectively. This demonstrated that the main pathway of alanine synthesis was not altered in *ts3* cells. The rates of incorporation of radioactive amino acids and nucleosides were measured after a shift from 33 to 39 C for mutant and wild-type cells. Alanine incorporation decreased steadily with time in *ts3*, whereas in the wild-type incorporation increased for all precursors with time. This demonstrated the modification of an alanine-specific process in *ts3*. The thermal inactivation of L-alanyl-tRNA synthetase was investigated by exposing a "pH 5.2" fraction from mutant and wild-type cells to 40 C for varying periods and measuring residual activity. After 60 min at 40 C the activities of alanyl-tRNA synthetase were 5 and 78% for *ts3* and wild-type, respectively, demonstrating the thermolability of this enzyme in *ts3*. Study of the other aminoacyl-tRNA synthetases demonstrated the alanine specificity of this altered function.

- 7159 C1-ESTERASE INACTIVATORS AND C4 IN MALIGNANT DISEASES. (Eng.) Bach-Mortensen, N. (Children's Hosp. Fuglebakken, Copenhagen, Denmark); Osther, K.; Stroyer, I. *Lancet* 2(7933):499-500; 1975.

Sera from 100 cancer patients, 100 patients with nonmalignant disease, and from 100 healthy blood-donors were compared to detect changes in the serum content of C1-esterase inactivator (C1 i.a.) and C4. C1 i.a. and C4 concentrations were estimated by Laurell rocket immunoelectrophoresis. No significant difference was found in the range of serum C1 i.a. and C4 levels between the blood-donors and patients with non-malignant diseases. However, the patients with malignant disease (mostly carcinomas, some malignant lymphomas and leukemias, and a few sarcomas) frequently had considerably higher serum C1 i.a. and C4 levels. Elevations of C1 i.a. were also noted in patients with certain virus diseases, such as mononucleosis, and type-II hereditary antineurotic edema. In virus disease, C1 i.a. generally returned to normal values after recovery. Increased values of serum C1 i.a. and C4 indicate a malignant disease if virus infection can be excluded or if raised values persist. Serological comparisons were also made using immunodiffusion with sheep anti-human C1 i.a.c. antiserum. Lower values of C1 i.a. and C4 were found in cancer patients during effective cytostatic treatment, whereas increasing values warned of relapse. Falling values were also observed after surgical removal of cancer. The authors suggest that the serum concentrations of C1-esterase inactivators and C4 reflect the activity of the disease.

- 7160 HYPERLIPIDEMIA AND TUMORS: POST-HEPARIN LIPASE ACTIVITY OF HAMSTER WITH MALIGNANT LYMPHOMA. (Fre.) Beaumont, V. (Unite de Recherche sur l'Atherosclerose de l'INSERM, Hopital Henri-Mondor, 94010 Creteil, France); Berard, M.; Boissier, C.; Beaumont, J.-L. *C. R. Acad. Sci. (Paris)* 280(5):665-668; 1975.

Post-heparin plasma lipase activity (PHPL) and triglyceride blood levels were correlated with the growth of transplanted Green lymphomas in hamsters. The determination of lipase activity was based on the ability of heparinized plasma to release labeled (^{14}C) fatty acids from a purified lipid substrate. The PHPL levels measured in five hamsters on the 15th day after graft, when hyperlipidemia was maximum, were much lower than in controls. In another group of 16 hamsters grafted with Green lymphomas, the triglyceride and PHPL levels were measured 5, 10, 15, and 20 days posttransplantation. Triglyceride blood levels greatly increased on the 10th day when tumors became palpable, and reached a maximum by day 15. PHPL was normal until the 10th day and markedly decreased between the 10th and 15th day. The results demonstrate that hyperlipidemia following transplant of the Green lymphoma in hamsters is characterized by high levels of triglycerides and low PHPL activity. The authors postulate that an anti-heparin or anti-lipase immunoglobulin is released from the tumor as a result of tumor growth in both the experimental animal and man.

- 7161 NEOPLASTIC TRANSFORMATION-LINKED ALTERATIONS IN ADENYLOSUCCINATE SYNTHETASE ACTIVITY. (Eng.) Jackson, R. C. (Indiana Univ. Sch. Medicine, Indianapolis, Indiana 46202); Morris, H. P.; Weber, G. *Biochem. Biophys. Res. Commun.* 66(2):526-532; 1975.

Adenylosuccinate synthetase was measured in normal, differentiating, and regenerating ACI/N rat liver, in transplantable hepatomas of different growth rates, in kidney cortex, and in a transplantable kidney tumor. The activity was increased to 1.6 to 3.7-fold in all tumors. The activity showed no correlation with the degree of histological or biochemical differentiation of the tumors, nor with their growth rate. Adenylosuccinate synthetase activity in regenerating liver was unchanged, and in neonatal liver it was much lower than in adult liver. It is concluded that the ubiquitous increase of this enzyme activity in the tumors of liver and kidney was linked with the neoplastic transformation.

- 7162 HYPOXANTHINE PHOSPHORIBOSYLTRANSFERASE ACTIVITY IN NORMAL, DEVELOPING, AND NEOPLASTIC TISSUES OF THE RAT. (Eng.) Wohlhueter, R. M. (Indiana Univ., Sch. Medicine, Indianapolis, Indiana). *Eur. J. Cancer* 11(7):463-472; 1975.

The tissue distribution of hypoxanthine phosphoribosyltransferase (HPRT) in a kinetic comparison of normal and neoplastic versions of the enzyme, and the modulation of HPRT activity as a necessary accessory to rapid cell proliferation are considered. Normal male rats and rats containing hepatoma were the subjects of the comparison study. Tissue homogenates were centrifuged and the supernatant assayed for enzyme activity. Assay of HPRT was based on the separation of product [^{14}C] nucleotide from substrate [^{14}C] base by binding the former on ion exchanger (PEI-cellulose). The reaction mixture included 0.2 mM [^{14}C]hypoxanthine and 0.2 mM

phosphoribosylpyrophosphate (PRPP). The velocity of the HPRT reaction was a linear function of tissue supernatant from both normal liver and Morris hepatoma 3924 A, with the velocity in normal liver somewhat higher. The pH profiles of activity in supernatants from liver hepatoma 3924 A were similar. PEI-bound radioactivity in which 44% of the initial hypoxanthine had been converted to PEI-bound material, proved to be 92% inosine monophosphate and 4% each of AMP and ADP. The initial reaction velocity of HPRT relative to PRPP and hypoxanthine concentration was similar with rat liver and hepatoma 3924 A. Half maximal velocities were attained at 4 μM hypoxanthine and 5 μM PRPP. HPRT was found in all tissues. Total liver enzyme activity and activity per average cell, were not influenced by the developmental growth curve of the rat. The administration of the artificial glucocorticoid triamcinolone was of no consequence in food-deprived rats whose liver activity had fallen to 15%. Finally HPRT activity in the 24 hr regenerating liver and the control (sham-operated rats) was the same.

- 7163 IMMUNOLOGICAL CHARACTERIZATION OF ONCOFETAL ALKALINE PHOSPHATASES FROM HUMAN PLACENTA AND HeLa₇₁ CELLS. (Eng.) Ghosh, N. K. (New York Univ. Med. Cent., N.Y.); Cox, R. P. *Enzyme* 20(1):35-45; 1975.

Several common genetic and molecular weight variants of human placental alkaline phosphatase (AP) were compared to one another and to the enzyme derived from HeLa₇₁ cells using antisera against both placental and HeLa₇₁ enzymes. Alkaline phosphatase antigen was purified from a single placenta by homogenization with 50 mM/l of Tris-HCl buffer, extraction with *n*-butanol, ammonium sulfate fractionation, exposure to heat, and Sephadex G-200 filtration. Purification of AP from confluent monolayers of HeLa₇₁ cells was achieved by homogenization, butanol extraction and gel filtration on a Sephadex G-200 column. Two New Zealand rabbits were injected s.c. with preparations containing one of the antigens (310 μg protein for the placental AP rabbit and 125 μg protein for the HeLa₇₁ AP/rabbit). Antiserum against placental AP precipitated 90% of the enzyme and the catalytic activity was quantitatively recovered in the antigen-antibody precipitate. Enzyme-antibody complexes failed to migrate on starch gel electrophoresis. Antiserum against placental AP cross-reacted with HeLa₇₁ AP and HeLa₇₁ AP antiserum reacted with the placental enzyme. Immunological analysis by double diffusion in agar showed that the three common genetic variants of placental AP (F, FS, and S) and the HeLa₇₁ AP were closely related when studied by antisera against both placental or HeLa₇₁ AP. When studied by immunodiffusion at pH 8.6 the genetic variants of human placental AP and the HeLa enzyme reacted with identity at the points of contact of the precipitation lines when precipitated by antisera against either enzyme. These findings support the view that the human placental and HeLa₇₁ APs are products of the same genetic locus. Derepression of a portion of the genome in association with malignant transformation might be responsible for ectopic production of this enzyme in HeLa₇₁ cells.

- 7164 TEMPERATURE SENSITIVITY OF CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE-BINDING PROTEINS AND THE REGULATION OF GROWTH AND DIFFERENTIATION IN NEUROBLASTOMA CELLS. (Eng.) Simantov, R. (Dep. Genetics, Weizmann Inst. Sci., Rehovot, Israel); Sachs, L. *J. Biol. Chem.* 250(9):3236-3242; 1975.

The relationship between cyclic AMP (cAMP)-binding proteins and cell growth and differentiation was studied in mouse neuroblastoma cells (C-1300) resistant to the toxic effects of dibutyl cAMP and prostaglandins E₁ and E₂ and in non-resistant C-1300 cells. The resistant cells had an increased tumorigenicity when injected s.c. in A/J mice and an increased saturation density and cloning efficiency in soft agar. In contrast to nonresistant cells, the resistant cells did not show induction of acetylcholinesterase activity, acetylcholine receptors, or the formation of axons by dibutyl cAMP and the prostaglandins. These differences were not associated with differences in cAMP content during cell growth or with differences in cAMP after prostaglandin treatment. Fractions, from DEAE-cellulose chromatography, with the highest binding capacity for cAMP (determined on 0.45 μ M nitrocellulose filters) were referred to as cAMP-binding proteins. The cAMP-binding proteins from resistant cells were more sensitive to temperature than those from nonresistant cells. Incubation at 37 C decreased both the apparent association constant and the specific activity of cAMP binding to proteins from resistant cells by about 50%, whereas the binding capacity and affinity of proteins from nonresistant cells were unaffected. The temperature-sensitive proteins were more resistant to temperature in the presence of β -mercaptoethanol and the temperature-resistant proteins were more temperature-sensitive in the presence of 5,5'-dithiobis(2-nitrobenzoic acid). The increased temperature sensitivity of cAMP-binding proteins in resistant cells was associated with decreased protein kinase activity. In the presence of cAMP or β -mercaptoethanol, the kinase activity increased 4- to 6-fold in the resistant cells and about 2-fold in the nonresistant cells. The temperature sensitivity of cAMP-binding proteins may affect the regulation of protein kinases, and this may be involved in the control of growth and differentiation in neuroblastoma cells.

- 7165 INCREASED URINARY EXCRETION OF CYCLIC GUANOSINE MONOPHOSPHATE IN RATS BEARING MORRIS HEPATOMA 3924A. (Eng.) Murad, F. (Dept. Internal Medicine, Univ. Virginia, Charlottesville, Va. 22903); Kimura, H.; Hopkins, H. A.; Looney, W. B.; Kovacs, C. J. *Science* 190(4209):58-60; 1975.

The urinary excretion of cyclic guanosine monophosphate (cGMP) was studied in female AC1 rats bearing Morris hepatoma 3924A. Animals were treated by local x-irradiation with 250 kv-peak, 800 R/min (total dose of 3750 R), 14 days after tumor implantation or were injected ip with 5-fluorouracil (150 mg/kg) 21 days after tumor implantation. In other experiments, 38 days after tumor implantation, rats either had their tumors excised or were given a sham operation. Urine was collect-

ed daily from experimental and control (without tumors) rats and assayed for cGMP and cyclic adenosine monophosphate (cAMP). Within several weeks after tumor inoculation, GMP excretion increased significantly. With progressive tumor growth, cGMP secretion continued to increase. After 46 days with the tumor, urinary cGMP was 68.5 ± 15.5 mole/g (a 21-fold increase over normal). Irradiation delayed both tumor growth and the increase in cGMP excretion. The administration of 5-fluorouracil also delayed tumor growth and the increase in cGMP excretion. Within one day after tumor excision, cGMP excretion fell to the normal range. Cyclic GMP excretion continued to increase in the sham-operated animals. No alterations in cAMP excretion were observed under any of the conditions examined. The authors conclude that tumor size and cGMP excretion are correlated and that cGMP excretion is useful as an index of tumor growth and regression.

- 7166 REGULATION OF ADENOSINE 3':5'-MONOPHOSPHATE EFFLUX FROM RAT GLIOMA CELLS IN CULTURE. (Eng.) Doore, B. J. (Dept. Biol., John Muir Coll., Univ. California San Diego); Bashor, M. M.; Spitzer, N.; Mawe, R. C.; Saier, M. H., Jr. *J. Biol. Chem.* 250(11):4371-4372; 1975.

Characteristics of cyclic AMP transport in a rat glial tumor cell line are presented. C-6 rat glioma cells were grown as confluent cultures, and cyclic AMP efflux rates were measured after 20-min intervals. Addition of β -agonistic catecholamines to the medium resulted in as much as a 300-fold increase in net cyclic AMP production. Agents such as valinomycin, oligomycin, and carbonyl cyanide *p*-trifluoromethoxyphenylhydrazone that reduced cellular ATP levels (to 15%, 56%, and 48%, respectively), also reduced cyclic AMP efflux (to 32%, 52%, and 47%, respectively). Secretion of cyclic AMP was also prevented by prostaglandin A₁ and pharmacological agents including probenecid and papaverine. Of the latter agents, only papaverine reduced ATP levels. These results suggest that the transport of cyclic AMP across animal cell membranes is energy-dependent and subject to regulation.

- 7167 CELL-SERUM FACTOR INTERACTION: CHARACTERISTICS OF STIMULATION OF PROTEIN SYNTHESIS IN EHRlich ASCITES CELLS BY FACTORS IN SERUM AND IN CELL EXTRACTS. (Eng.) Kaminskas, E. (Mount Sinai Medical Center, 948 North Twelfth St., Milwaukee, Wis. 53233). *Exp. Cell Res.* 94(1):7-14; 1975.

Conditions that determine the extent of stimulation of protein synthesis in Ehrlich ascites cells by factors in serum and in cell extracts were studied. Stimulation of protein synthesis induced by serum in serum-starved (0.5% serum, 24 hr) Ehrlich ascites tumor cells was directly proportional to the concentration of added heat-inactivated calf serum, inversely proportional to the concentration of cells in the culture, and dependent on the length of exposure of cells to serum. Stimulation was markedly decreased in cells incubated with serum at tempera-

tures lower than 37 C. During exposure of cells to serum, active protein synthesis was not required in order for subsequent stimulation of protein synthesis to take place. These characteristics were consistent with the possibility that stimulation of protein synthesis followed uptake of serum factors by cells. Extracts of cells stimulated protein synthesis in a similar fashion to serum. Stimulations by extracts and by serum were additive. The factors in cell extracts were macromolecular, associated with particulate fractions, and inactivated by trypsin, but not by RNAase, DNAase, ether or chloroform. Extracts of serum-grown cells were more stimulatory than extracts of serum-starved cells. When serum-starved cells were incubated with serum, stimulatory activities of their extracts increased as a function of time of incubation with serum. Because the stimulation of protein synthesis was directly proportional to serum concentration and inversely proportional to cell concentration, the cells appear to interact with serum factors in a stoichiometric fashion.

- 7168 ISOLATION OF A CATIONIC POLYPEPTIDE FROM HUMAN SERUM THAT STIMULATES PROLIFERATION OF 3T3 CELLS. (Eng.) Antoniadis, H. N. (Harvard Univ., Sch. of Public Health, Boston, Mass. 02115); Stathakos, D.; Scher, C. D. *Proc. Natl. Acad. Sci. USA* 72(7):2635-2639; 1975.

The isolation from whole human serum of a cationic polypeptide that stimulates proliferation in confluent populations of 3T3 cells is reported. Pooled human serum was subjected to ion-exchange chromatography and the portion containing the growth factors and insulin-like activity was lyophilized, dialyzed, and eluted on a Sephadex G-100 column. The Sephadex fractions were then subjected to isoelectric focusing on polyacrylamide gels and the fractions obtained by isoelectric focusing were subjected to sodium dodecyl sulfate electrophoresis. After each step, the various fractions were injected into Balb/c rats to determine insulin-like activity. They were also added to confluent cultures of Balb/c-3T3 cells, along with [³H]thymidine to determine their ability to stimulate DNA synthesis and cell division. The addition of whole human serum to confluent 3T3 cultures stimulated proliferation, the serum factor(s) that stimulated this proliferation being almost completely removed by a Dowex resin. Dowex treatment of whole serum allowed the recovery of 8 mg of protein from 7 g of whole serum protein. The serum fraction eluted from the Dowex resin also contained the factors with insulin-like activity. Incubation of the Dowex-absorbed protein with trypsin or chymotrypsin caused a loss in the ability to stimulate DNA synthesis; heat had no such effect, but reduction with mercaptoethanol did. The Dowex-absorbed fractions with the greatest DNA-stimulating and insulating and insulin-like activities were present in Sephadex fraction IV, and some DNA-stimulating activity was present in Sephadex fraction V. On isoelectric focusing, the DNA-stimulating activity focused in an area corresponding to pH 9.6-9.8, while the insulin-like activity focused in the range 7.3-9.4. The molecular weight of the pI 9.7 fraction was 13,000. Approximately 10⁷ molecules of the polypeptide in 0.2 ml of growth medium

allowed the replication of one density-inhibited cell. The results indicate that at least one human serum growth factor is distinct and can be separated from the heterogeneous group of serum polypeptides with insulin-like activity.

- 7169 COMPARATIVE STUDY OF THE AMINO ACID COMPOSITION OF SOME TUMOR AND NORMAL MELANOSOMES. (Eng.) Borovansky, J. (Faculty Medicine, Charles Univ., 128 53 Prague, Czechoslovakia); Duchon, J. *Neoplasma* 22(2):195-199; 1975.

The amino acid composition of melanosomes isolated from Harding-Passey mouse melanoma, metastases of human malignant melanoma, and pigmented tissue of cattle eyes was studied. All melanosomes studied consisted of 18 amino acids plus 3,4-dihydroxyphenylalanine. The amino acid composition of both melanomas was similar; however, the melanosome from the bovine eye had a significantly higher glycine content. An inverse relationship of lysine and melanin content was noted; lysine content decreased in the order Harding-Passey melanoma melanosomes > human melanoma melanosomes > human melanoma melanosomes > cattle eye melanosomes. From the sum of micromoles of asparagine, glutamic acid, lysine, serine, arginine, threonine, valine, leucine, isoleucine, methionine, proline, and phenylalanine, the Hatch polar/apolar ratio of the melanomas was calculated as < 1.30. Thus, they were assigned to the group of proteins with a large proportion of apolar residues. The higher level of cysteine and lysine in the melanoma hydrolysate supported the theory of special matrix protein in melanosomes. It is suggested that such amino acid analyses could be used in studying the morphological deviations and structural proteins of melanosomes.

- 7170 THE SIGNIFICANCE OF SERUM PROGESTERONE AND SERUM UNCONJUGATED OESTRADIOL-17 β IN UNABORTED HYDATIDIFORM MOLE. (Eng.) Dawood, M. Y. (New York Hosp.-Cornell Medical Center, 525, East 68th St., New York, N.Y. 10021). *Acta Endocrinol. (Kbh.)* 79(4):729-739; 1975.

Both serum progesterone and serum unconjugated estradiol-17 β (E₂) were measured by competitive protein binding assay and radioimmunoassay respectively in 42 cases of unaborted hydatidiform mole. Serum human chorionic gonadotropin (HCG) was measured by a hemagglutination-inhibition technique. In 26 cases of intact molar pregnancies without theca lutein cysts (TLC), serum progesterone ranged from 18.0 - 289.0 ng/ml with a mean \pm standard error of the mean (SEM) of 65.9 \pm 13.1 ng/ml. Serum E₂ ranged from 4.0 - 37.0 ng/ml with a mean \pm SEM of 17.9 \pm 1.9 ng/ml. Serum HCG ranged from 60 - 1,920 IU/ml with a mean \pm SEM of 531.5 \pm 105.7 IU/ml. In contrast, 16 cases of intact molar pregnancies with TLC had serum progesterone ranging from 34.1 - 288.0 ng/ml with a mean \pm SEM of 134.1 \pm 2.4 ng/ml; serum E₂ ranging from 1.7 - 76.3 ng/ml with a mean \pm SEM of 31.5 \pm 5.3 ng/ml, and serum HCG ranging from 320 - 2,560 IU/ml with a mean \pm SEM 1,400 \pm 196.2 ng/ml. The differences between the mean of these three hormones in hydatiform mole with and without TLC were signifi-

cant (progesterone: $P < 0.005$; E_2 : $P < 0.0125$; HCG: $P < 0.005$). There was a significant correlation between serum HCG and serum E_2 (coefficient of correlation $r = +0.3565$, $P < 0.0125$) and between serum E_2 and serum progesterone ($r = +0.3787$, $P < 0.0125$). There was no significant difference in the mean levels of serum progesterone, E_2 and HCG in hydatiform mole with and without subsequent malignant sequelae. The mean ratios of E_2 to progesterone were essentially similar in moles with and without TLC and with and without malignant sequelae. The findings of both elevated serum E_2 and serum progesterone in molar pregnancy and the highly significant correlation between serum E_2 and progesterone suggest that progesterone is produced primarily by the molar tissue albeit some from the ovary.

- 7171 EFFECT OF TESTOSTERONE AND ESTRADIOL-17 β ON SYNTHESIS OF DNA, RNA AND PROTEIN IN HUMAN BREAST IN ORGAN CULTURE. (Eng.) Finkelstein, M. (Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Geier, A.; Horn, H.; Levi, I. S.; Ever-Hadani, P. *Int. J. Cancer* 15(1):78-90; 1975.

The effects of testosterone and estradiol 17 β on DNA, RNA, and protein synthesis were studied in explants of seven cases of cystic mastitis, 8 cases of fibroadenoma, 17 cases of primary cancerous lesion, and 8 cases in which uninvolved tissue was taken as far as possible from the carcinoma at the time of mastectomy. Explants from human female breasts were incubated with concentrations of 6.9×10^{-5} M testosterone and with estradiol-17 β , 3.6×10^{-6} M. After an initial 72 hr incubation at 37 C, the explants from each dish were transferred to a second dish containing 1.5 ml of medium supplemented with ^3H -thymidine (2 $\mu\text{Ci/ml}$), ^3H -uridine (0.5 $\mu\text{Ci/ml}$) and ^{14}C -L-amino acid mixture (0.5 $\mu\text{Ci/ml}$) and were then incubated for an additional 48 hr. After 5 days of incubation, estimates of the synthesis of DNA, RNA, and protein were calculated and assessed microscopically. In tissue from patients with cystic mastitis, testosterone and estradiol-17 β inhibited the incorporation of ^3H -thymidine into DNA. Testosterone uniformly inhibited the incorporation of ^3H -uridine into RNA and of ^{14}C -L-amino acids into protein. In contrast, estradiol-17 β inhibited the synthesis of RNA and protein in two cases, enhanced the synthesis of RNA and protein in three cases, and no effect was obtained in the two other cases. In all samples of fibroadenoma grown in organ culture with testosterone, the synthesis of DNA, RNA and protein was inhibited. Estradiol-17 β inhibited the synthesis of DNA in seven out of eight cases. The effect of estradiol-17 β on the synthesis of RNA and protein was not consistent: increased in five cases, inhibited in one, and no change in two. In tissue from patients with carcinoma, the effect of testosterone on DNA was inhibitory in nine cases, stimulative in four cases, and ineffective in four. Estradiol-17 β stimulated DNA synthesis in nine cases, inhibited it in six cases; and regressive changes were observed in two cases. The effect of the steroids on the explants of uninvolved tissue was variable and did not always parallel their effect on the cancerous tissue from the respective patients.

- 7172 REVERSIBLE ARREST OF MOUSE 3T6 CELLS IN G₂ PHASE OF GROWTH BY MANIPULATION OF A MEMBRANE-MEDIATED G₂ FUNCTION. (Eng.) Shodell, M. (Imperial Cancer Res. Fund, PO Box 123, Lincoln's Inn Fields, London WC2A 3PX, England). *Nature* 256(5518):578-580; 1975.

A method by which mouse 3T6 cells can be reversibly arrested during the G₂ phase of cell growth and a possible cause are discussed. Cells were seeded in the absence of serum and incubated at 37 C for three days. The G₁ arrested cultures were transferred to rich serum conditions in the presence of 2.88 mM hydroxyurea holding the cells just at the entry of DNA synthesis. After incubation for 15 hr, cells were placed in serum-rich, hydroxyurea-free medium. In this way presynchronization was achieved. Cells were incubated again for 9.5 hr at 37 C before being subjected to 15 C. After two durations of 20 and 68 hr the cells were returned to 37 C where mitotic responses could be followed cinemicrographically. In both cases there was a lag of about two hours before any mitoses were apparent, followed by a sharp mitotic burst at 3-4 hr after returning to 37 C. Different time periods at 15 C did not affect the two-hour lag. The DNA content of cells cultured at 15 C, measured on a BDH flow microfluorimeter, was highest in the G₂ region (80%), in contrast to the amount of DNA in the G₂ phase of randomly growing cells (17%). Assuming that the G₂ arrest is the function of the fluidity of some cellular membrane system, then maintaining fluidity even at 15 C would enable the cells to achieve mitosis. 3T6 cells were grown in (acetone precipitated) serum with an additional amount of biotin. Saturated palmitate and stearate fatty acids in the cells grown in delipidated serum (delipidated cells) had increased three-fold, whereas unsaturated fatty acids increased 2.5-fold, compared with cells grown in whole serum. A portion of these cells were presynchronized and incubated at 15 C. The DNA content/cell profile for randomly growing delipidated cells and the cells transferred to 15 C were similar. This indicated that cells with altered fatty acid composition were not held in G₂ at 15 C.

- 7173 THE RELATIONSHIP BETWEEN TUMORIGENICITY, GROWTH IN AGAR AND FIBRINOLYTIC ACTIVITY IN A LINE OF HUMAN OSTEOSARCOMA CELLS. (Eng.) Jones, P. A. (Children's Hosp. Los Angeles, 4650 Sunset Blvd., Los Angeles, Calif. 90027); Rhim, J. S.; Isaacs, H., Jr.; McAllister, R. M. *Int. J. Cancer* 16(4):616-621; 1975.

The effects of type-C transforming or transformation-defective virus information into human osteosarcoma cells (TE-85), and the isolation of a clone with high levels of fibrinolytic and tumorigenic activity, were studied. Some TE-85 cell clones (clones 2, 4 and 6) showed increased fibrinolytic activity but did not form tumors in antithymocyte serum (ATS)-treated hamsters. TE-85 cells infected with mammalian transformation-defective viruses showed low (FeLV) or increased (RD-114 virus) levels of fibrinolytic activity and did not form tumors in hamsters. TE-85 cells either nonproductively

infected with Ki-MSV or productively infected with M-MSV (RD-114), had fibrinolytic activity and did form tumors (12 of 13, and 14 of 14 respectively) in hamsters. The MSV gene(s) but not colony formation in agar or extracellular fibrinolytic activity appears to be capable of rendering TE-85 cells tumorigenic in ATS-treated hamsters.

7174 SELECTIVE GROWTH OF MALIGNANT CELLS BY *IN VITRO* INCUBATION ON TEFLON. (Eng.)

Paranjpe, M. S. (Nat'l. Cancer Inst., Nat'l. Inst. Health, Bethesda, Md. 20014); Boone, C. W.; del Ande Eaton, S. *Exp. Cell Res.* 93(2):508-512; 1975.

The use of Teflon as a substrate for determining the anchorage dependence of cultured cell lines and as a selective substrate for the growth of transformed cell lines were investigated. The A31 clone of mouse BALB/3T3 and the SV3T3 line of simian virus-transformed BALB/3T3 cells were used as corresponding neoplastic and non-neoplastic lines. Non-malignant lines did not exhibit significant cell growth on Teflon, whereas the neoplastic lines grew to high densities. BALB/3T3 grew from a seeding of 1.6×10^4 cells to saturation density (6×10^4 cells/cm²) by the sixth day in control petri dishes; however, in Teflon, fewer than 20% of the cells had undergone one division by the sixth day (final cell count, 2.0×10^4 cells/cm²). Cell visibility in BALB/3T3 cells after growth on Teflon was greater than 90% 24 and 48 hr after seeding. The virally-transformed SV3T3 line reached a high saturation density on both plastic and Teflon substrates. The neoplastic mouse cell line T238 grew to a density of more than 26×10^4 cells/cm² by day seven on both Teflon and plastic. Similar experiments were performed with mouse cell lines ACT, P-2 and ACT, P-10. ACT, P-10 cells (tumorigenic) grew readily on both substrates. ACT, P-2 (non-tumorigenic) cells failed to grow on Teflon but formed a confluent monolayer on plastic. Human W138 cells planted on Teflon were incapable of mitosis, but on the plastic substrate, the doubling time was about 24 hr. Two human cells derived from a melanoma and from a kidney carcinoma increased in numbers on Teflon substrates. The authors conclude that there was a definite correlation between the neoplastic character of the cells and their ability to grow and divide on Teflon.

7175 FRACTIONATION OF NUCLEI AND ANALYSIS OF NUCLEAR PROTEINS OF RAT LIVER AND MORRIS HEPATOMA 7777. (Eng.) Wilson, B. (Rockefeller Univ., New York, N.Y. 10021); Lea, M. A.; Vidali, G.; Allfrey*, V. G. *Cancer Res.* 35(11/Part 1): 2954-2958; 1975.

The contributions of nuclear populations in the total profile of nuclear proteins in a tissue were examined in normal male Buffalo rat liver and Morris hepatoma 7777. Comparison by sodium dodecyl sulfate polyacrylamide gel electrophoresis of phenol-soluble nuclear proteins from tumor and control liver revealed additional proteins of molecular weight 60,000, 100,000, and 135,000 and the loss of proteins of about 45,000 and 55,000 in the tumor. Subfractionation of liver nuclei on a 30-50% sucrose

gradient yielded three nuclear classes with nearly identical complements of the phenol-soluble proteins. Similar fractionation performed on the hepatoma nuclei also produced three nuclear populations. In the hepatoma nuclei, several differences in the phenol-soluble proteins were found between the minor, slowly sedimenting nuclear fraction, and the two major fractions, while the two latter fractions were very similar in their protein composition. Histones derived from both tissues were also compared electrophoretically, indicating a decrease in the concentration of the minor histone fraction H1^o in all nuclear classes derived from the tumor.

7176 ROLE OF MICROVILLI IN SURFACE CHANGES OF SYNCHRONIZED P815Y MASTOCYTOMA CELLS.

(Eng.) Knutton, S. (Dept. Biochemistry, Univ. Oxford, Oxford, England); Sumner, M. C. B.; Pasternak, C. A. *J. Cell Biol.* 66(3):568-576; 1975.

The surface morphology of synchronized P815Y mastocytoma cells was examined by scanning electron microscopy. Early G₁ cells were found to be comparatively smooth or lightly villated, whereas at later stages the surface became progressively more villated. In G₁ cells, most microvilli had a uniform diameter; in S and G₂ cells, many microvilli showed branching and often originated from much larger surface protuberances. Small "blebs" were seen on the surface of many cells but these structures did not appear to be a characteristic feature of cells at any one stage of the cell cycle. The presence of microvilli increases the total surface of the cell to such an extent that the ratio of volume to surface area remains constant throughout the cell cycle. The mechanism of cytokinesis is thus a physical one, involving the unfolding of previously accumulated microvilli.

7177 NORADRENALINE INDUCES MORPHOLOGICAL ALTERATIONS IN NUCLEATED AND ENUCLEATED RAT C6 GLIOMA CELLS. (Eng.) Oey, J. (Universitat Konstanz, Fachbereich Biologie, D-775 Konstanz, West Germany).

Nature 257(5524):317-319; 1975.

7178 QUANTITATIVE ULTRASTRUCTURAL STUDY OF THE ADRENAL CORTEX: EFFECTS OF A MAMMOTROPIC PITUITARY TUMOR PRODUCING GROWTH HORMONE AND PROLACTIN (MtT-W10), AND OF INJECTED GROWTH HORMONE IN THE RAT. (Eng.) Nickerson, P. A. (Dept. Pathology, State Univ. New York at Buffalo, N.Y. 14207). *Betr. Pathol.* 154(1):52-62; 1975.

7179 *IN VITRO* RESPONSES OF PIGMENTARY SYSTEM OF MOUSE MELANOMA TO α -MELANOCYTE-STIMULATING HORMONE AND 3',5'-CYCLIC ADENOSINE MONOPHOSPHATE. (Eng.) Lee, T. H. (Veterans Adm. Hosp., Bronx, N.Y.); Lee, M. S. *Fed. Proc.* 34(3):693; 1975.

7180 CHOLESTEROL AND PHOSPHOLIPID CONTENT OF 3T3 CELLS AND TRANSFORMED DERIVATIVES. (Eng.) Adam, G. (Fachbereich Biologie, Universitat Konstanz,

- Switzerland); Alpes, H.; Blaser, K.; Neubert, B. *Z. Naturforsch.* [C] 30(9/10):638-642; 1975.
- 7181 INVESTIGATIONS ON SPECIFIC STEROID BINDING COMPONENTS FROM HUMAN KIDNEY AND RENAL CELL CARCINOMA [abstract]. (Eng.) Bojar, H. (Institut fur Physiologische Chemie II, Universitat Dusseldorf, West Germany); Dreyfurst, R.; Balzer, K.; Doscher, D.; Staib, W. *Acta Endocrinol.* [Suppl.] (Kbh.) 199:130; 1975.
- 7182 METABOLISM OF STEROID HORMONES IN A VIRILIZING ADENOMA OF ADRENAL CORTEX [abstract]. (Eng.) Lisboa, B. P. (Universitäts-Frauenklinik Eppendorf, Hamburg, West Germany); Strassner, M.; Nocke-Finck, L.; Breuer, H.; Bayer, J. M. *Acta Endocrinol.* [Suppl.] (Kbh.) 199:395; 1975.
- 7183 DEFECTIVE THYROGLOBULIN SYNTHESIS IN AN EXPERIMENTAL RAT THYROID TUMOR: IODINATION AND THYROID HORMONE SYNTHESIS IN ISOLATED TUMOR THYROGLOBULIN. (Eng.) Monaco, F. (Centro della Tiroide c/o IIA Clinica Medica dell'Universita, Policlinico Umberto I, 00100 Rome, Italy); Grimaldi, S.; Dominici, R.; Robbins, J. *Endocrinology* 97(2):347-351; 1975.
- 7184 DIETARY ALTERATION OF FATTY ACID COMPOSITION OF LIPID CLASSES IN MOUSE MAMMARY ADENOCARCINOMA. (Eng.) Rao, G. A. (Veterans Administration Hosp., Martinez, Calif. 94553); Abraham, S. *Lipids* 10(10):641-643; 1975.
- 7185 LEVELS OF CHOLESTEROL, 11-HYDROXYCORTICOSTEROIDS AND PROGESTERONE IN PLASMA FROM POSTMENOPAUSAL WOMEN WITH BREAST CANCER. (Eng.) Smethurst, M. (Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, Great Britain); Basu, T. K.; Williams, D. C. *Eur. J. Cancer* 11(10):751-755; 1975.
- 7186 CORTICOSTERONE AS A LIVER CELL SYNCHRONIZER. (Ger.) Desser-Wiest, L. (Institut fur Krebsforschung der Universitat Wien, Vienna, Austria). *Oesterr. Z. Onkol.* 2(2/3):56-59; 1975.
- 7187 SERUM FERRITIN LEVELS IN PATIENTS WITH BREAST CANCER [abstract]. (Eng.) Marcus, D. M. (Albert Einstein Coll. Med., Bronx, N.Y.); Zinberg, N. *Clin. Res.* 23(3):447A; 1975.
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AARONSON, S.A.
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BEPLIE, J. 7122	BEONE, C.W. 6797*, 6911*, 7174	BURNS, F.J. 6835
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BO CHEN, L. 6838	BRUNET, M. 7122	CATER, C.M. 6672
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BOIRON, M. 7047*	BUCHANAN, J.M. 6838	CHAIT, A. 7061
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DOSCHER, D. 7181*	ENZAN, H. 6763*	FRANCKE, B. 6857
DRACH, J.C. 6690	ERIKSSON, S. 7042*	FRAPPIER-DAVIGNON, L. 7150*
DREWINKO, B. 7002*	ERSLEV, A.J. 6636	FRASH, V.N. 6751*
DREYFURST, R. 7181*	ESCUDEO BARRILERO, A. 7070*	FRAUMENI, J.F., JR. 7095*
DUBININ, N.P. 6849	ESHEL, I. 6951	FRAUMENI, J., JR. 7054*
DUCHON, J. 7169	ESTES, M.K. 6617	FREEMAN, A.E. 6770*
DUELL, E.A. 6664*	EVER-HADANI, P. 7171	FREEMAN, C. 7025
DUESBERG, P.H. 6837	EVERALL, J. 7143*	FREI, J.V. 6779*
DUGAN, L.R., JR. 6787*	FAHMY, M.J. 6696	FREUDENTHAL, R.I. 6686
DULBECCO, F. 6620	FAHMY, O.G. 6696	FRIEDMAN, M.A. 6697, 6757*
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DVORAK, H.F. 6625	FENNELL, D.I. 6673	FU, Y.-S. 7107*
DVORAK, R. 7092*	FERGUSON, L.N. 6605	FUJIMAKI, M. 6765*
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EARLE, J. 6651*	FERNANDES, G. 6973*	FUJIWARA, Y. 6706
EASTY, G. 7101*	FERNANDEZ, F. 6711	FUKUHARA, M. 6722*
EBBESEN, P. 7194*	FERNANDEZ ROJO, F. 7070*	FUKUOKA, M. 6736*
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EBINGER, G. 7048*	FIEL, R.J. 6921*	GADBOIS, D.F. 7128
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- HARRINGTON, J.S.
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- HARRIS, A.W.
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- HARRIS, C.
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HARRISON, F.R. 7155	HCEFFMAN, C.R. 6910*	IHLE, J.N. 6948
HARTWICH, G. 7088*	HCLDEN, H.T. 6952	IL'IN, K.V. 6895
HASELTINE, W.A. 6842	HCLLANDER, M.M. 6934	IMAMURA, A. 6759*
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HATANAKA, Y. 6736*	HCLMES, E.C. 6998*, 6999*	IOKI, Y. 6759*
HATZFELD, A. 6925	HONG, L. 6888	IRIE, R.F. 7006*
HAVERMAN, J. 6950	HONGO, J. 7035	IRVING, C.C. 6681
HAYAKAWA, K. 7035	HODKS, J.J. 6623	ISAACS, H., JR. 7173
HAYAKAWA, T. 6720	HOPKINS, H.A. 7165	ISAKA, H. 6924
HAYASHIDE, I. 6763*	HOPPER, J.E. 6944	ISELER, G. 7200*
HECKER, F. 6721	HORN, H. 7171	ISHIDA, Y. 6718
HEISE, H.W. 7123	HORNING, E.C. 6783*	ISHII, S. 7035
HELMKAMP, F.W. 6812*	HOUSE, S.B. 6987*	ISHIKAWA, K. 6741*
HEMPELMANN, L.H. 7125	HOWE, J.R. 6654*	ITAGAKI, A. 6862
HENDERSON, J.Y. 7147*	HOWELL, S.B. 7005*	ITO, Y. 6906*
HERBERMAN, R. 7054*	HRYNYSZYN, V. 6812*	IVANOV, V.L. 6994*
HERBERMAN, R.B. 6952	HSU, T.C. 7007	IWASHITA, H. 6729*
HEFSCHMAN, H.R. 7001*	HUANG, E.-S. 6844	IZRAEL, V. 7047*
HERZIG, G.P. 6987*	HUANG, G. 6794*	JACKSON, R.C. 7161
HESS, M.W. 6667*	HUE, G. 6953	JACOBBI, J. 6712
HIEMSTRA, K. 6968*	HUEBNER, R.J. 6874	JACOBS, B.B. 6961
HIGASHI, N. 7056*	HUGHES, R.G., JR. 6852	JACOBSON, W.C. 7140*
HIGGINS, I.T.T. 7110	HUHN, D. 7052*	JACQUILLAT, C. 7047*
HILGERS, J. 6950	HUMBERT, J.R. 7039	JAEGER, P. 6926
HILL, M.J. 6711	HLNTER, T. 6857	JAGO, M.V. 6682
HINO, S. 6883, 6884	HURWICH, B.J. 7061	JANIAUD, P. 6740*
HINUMA, Y. 6846, 6847	HUTCHESON, E.T. 6684	JANUNGER, K.-G. 7042*
HIRANANDANI, L.H. 7114	IAGUBOV, A.S. 6899*	JASMIN, C. 6868
HIPAC, K. 6781*, 6800*	IAKOVLEVA, L.A. 6892	JEANLOZ, P.W. 7193*
HIRDSE, F. 6764*	IASTREBOV, A.P. 6751*	JEEVES, I. 6705
HIRSCH, M.E. 6969*	ICHIKI, A.T. 7078*	JEFFERY, A.M. 6776*
HIPSCH, M.S. 6956, 6962	IDE, T. 6703	JELLINGER, K. 7091*
HO, L. 6878	IGEL, H.J. 6770*	JERINA, D.M. 6720, 6748*, 6776*
HOCHSTADT, J. 6901*	IGLESIAS, R. 6641	JOHNSON, C.A. 6609

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JOHNSON, R.T. 6907*	KELLER, S. 7050*	KLEINSCHUSTER, S.J. 6734*
JOHNSON, T.R. 6985*	KELLER, W. 6920*	KLEINSMITH, L.J. 6880
JOHNSTON, J.O. 7198*	KELLY, A.P. 6969*	KLEMM, V.G. 7045*
JONES, P.A. 6770*, 7173	KELLY, F. 6965	KLEMPERER, M.R. 6934
JORGENSEN, P.N. 6984*	KELSEY, W.H. 6664*	KLETZIEN, R.F. 7190*
KABAYASHI, H. 6865	KENDALL, A.B. 7019	KNAUF, S. 7003*
KAIGHN, M.E. 6679	KEPLINGER, M.L. 6791*	KNIGHT, R.A. 6949
KAITO, H. 6796*	KERN, C.H. 7004*	KNJAZEV, P.G. 6836
KAJIHARA, H. 6768*	KERSEY, J. 7089*	KNOX, E.G. 6606
KAKUBAVA, V.V. 6892	KETTMANN, R. 6912*	KNUTTON, S. 7176
KALASHNIKOV, V.V. 7058*	KEYS, T.F. 6917*	KOCISOVA, J. 7071*
KALCKAR, H.M. 6856	KHACHATURIAN, L.M. 6988	KOCSIS, J.J. 6610
KALEDIN, V.I. 6980*	KHARKOVA, E.N. 7149*	KODAMA, Y. 6768*
KALLISTRATOS, G. 6747*	KHARLAMOVA, S.F. 6754*	KODERA, Y. 6983*
KALLISTRATOS, U. 6747*	KHOLODNYI, M.D. 7191*	KOGAN, F.M. 6811*
KAMINSKAS, E. 7167	KILARSKI, W. 6881	KOHN, A. 7154
KANDA, H. 6718	KILLION, J.J. 6976*	KOKOSHA, L.V. 6892
KANJE, M. 7192*	KIM, E.B. 6874	KOLIADINA, I.P. 7058*
KAPLAN, E.L. 6806*	KIM, J. 7079*	KOLLMORGEN, G.M. 6976*
KARAKI, Y. 6765*	KIM, M. 7137	KONISHI, Y. 6781*, 6800*
KARANFILSKI, B.T. 6806*	KIMURA, G. 6862	KOONTZ, W.W. 7107*
KARMYSHEVA, V.IA. 6904*	KIMURA, H. 7165	KORDAC, V. 7073*
KASHII, A. 6741*	KIMURA, K. 6935	KOROSTELEVA, T.A. 6988
KATSUTA, H. 6964	KING, C.M. 6819*	KOROTKORUCHKO, V.P. 7195*
KATZE, J.R. 7156	KING, H.W.S. 6687	KOSHI, S. 7132
KAUFMAN, D. 6769*	KIRCHNER, H. 6952	KOSOWER, E.M. 6957
KAWABATA, H. 6781*, 6800*	KITAHARA, T. 6902*	KOSOWER, N.S. 6957
KAWAGUCHI, M. 6765*	KLEBANOFF, S.J. 6947	KOVACS, C.J. 7165
KAWAKAMI, M. 6763*	KLEIMAN, L. 7155	KOZAK, V.V. 6685
KAWANO, N. 6741*	KLEIN, D.L. 6971*	KOZLOV, A.P. 6836
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KAWAZOE, Y. 6794*	KLEIN, G. 6845, 6951	KRAEVSKII, N.A. 7058*
KAY, S. 7107*	KLEIN, P.A. 6960	KRAGTEN, M.C.T. 6689

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KRIVIT, W. 7089*	LEDERER, B. 7059*	LILLEHOJ, E.B. 6673
KRUGER, F.W. 7126	LEE, C.W. 7106*	LINDAHL, F. 7112
KUCERA, L.S. 6853	LEE, D.J. 6773*, 6774*	LINNA, T.J. 6744*
KULIK, V.A. 6685	LEE, J.A.H. 7138*	LISBOA, B.P. 7182*
KUMAR, V. 6622	LEE, J.C. 6948	LISCHKE, J.H. 7037
KURAHARA, C. 6863	LEE, M.S. 7179*	LITTLE, J.H. 6938
KURCYANAGI, M. 6736*	LEE, P.N. 6708	LITWIN, J.A. 6688
KUZNETSOV, O.K. 6836	LEE, R.E. 6801*	LLOYD, E.L. 6870
KUZUMAKI, N. 6865	LEE, T.H. 7179*	LLOYD, H.M. 6712
KWOCK, L. 6879	LEE, V. 7099*	LOKICH, J. 7072*
KYLE, P.A. 7016	LEISTENSCHNEIDER, W. 7027	LOKICH, J.J. 6733*
LAFONTAINE, N. 6989*	LENER, R.A. 6885	LOMSADZE, B.A. 6755*
LAGERHOLM, B. 7022	LERCY, P. 7131	LONG, L.A. 7013
LANDBECK, G. 7053*	LESHER, S. 6732*	LOONEY, W.B. 7165
LAPERTOSA, G. 7086*	LETT, J.T. 6612	LOPEZ BAREA, F. 7070*
LAPIN, B.A. 6892	LEVENBUK, I.S. 6904*	LOTLIKAR, P.D. 6680
LAPIS, K. 6841	LEVENTON-KRISS, S. 6850	LOUIT, J.F. 6870
LARRIPA, I. 7010, 7087*	LEVI-MONTALCINI, R. 6635	LOWE, W. 6707
LASKINA, A.B. 7135	LEVIJ, I.S. 7171	LOWRY, W.S. 6723*
LASNE, C. 6739*	LEVIN, W. 6748*	LOZZIO, B.B. 6996*, 7078*, 7079*
LATAPJET, R. 6810	LEVINE, A. 6619	LOZZIO, C.B. 6996*, 7078*, 7079*
LAUDER, I. 6707	LEVY, C.C. 6642	LUCKEY, T.D. 6668*
LAUG, W.E. 6770*	LEVY, J. 6913*	LUDELM, D.B. 6799*
LAURENT, F. 7122	LEVY, S. 6738*	LUM, L.C. 7030
LAVERGNE, E. 7150*	LEWIS, D.D. 7005*	LUMB, J.R. 6990*
LAW, F.C.P. 6690	LEY, R.D. 6825*	LUNDSTROM, R.C. 7128
LAW, L.W. 7005*	LI, F.P. 7095*, 7123	LUSCHER, E.F. 6997*
LAWMAN, M.J.P. 6854	LIBBEY, L.M. 6786*	LUSTIG, S. 6957
LE FRANCOIS, D. 6953	LICHTIGER, B. 7002*	LVOVA, G.N. 6849
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LEA, M.A. 7175	LIEBER, M. 6890	MACASAET, F.F. 6917*
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MAEKAWA, A.
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MAHER, V.M.
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MAIN, J.H.P.
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MAJOR, E.O.
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MAK, S.
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MAKAROV, G.V.
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MAKK, L.
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MANCUSO, T.F.
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MANEY, R.S.
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MARABELLA, P.C.
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MARPOVITS, P.
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MARTINEZ LASIERRA, M.
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MATSUO, Y.
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MATSUSHITA, H.
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MATTIL, K.F.
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MAURER, B.A.
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MAURUS, R.
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MAWE, R.C.
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MAYER, G.
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MAYER, R.T.
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MAYER, S.
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MAZURENKO, N.N.
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MCALLISTER, R.M.
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MCCORMICK, J.J.
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MCCOY, J.L.
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MCGINNIS, J.P., JR.
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MCGLASTAN, N.D.
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MCGUIRE, W.L.
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MEAD, M.L.
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MEARES, J.D.
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MEDLEY, G.
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MEDVEDCVSKII, A.G.
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MEEHAN, T.D.
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MEHNERT, W.H.
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MEHTA, J.R.
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MELVIN, P.
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MENARD, S.
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MENENDEZ, H.
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MERENDA, C.
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MERRILL, D.A.
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MERRILL, J.P.
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METAYER, J.
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METZLER, M.
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MICKEY, D.D.
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MIDORIKAWA, O.
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MIGAI, H.
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MILLER, J.A.
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MILLER, M.S.
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MILLER, R.G.
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MILLS, J.
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MILNE, E.N.C.
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MINKLER, J.
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MIROTVORTSEVA, K.S.
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MIRVISH, S.S.
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MITANI, S.
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MITCHELL, F.E.
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MITCHELL, M.S.
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MITSUNO, T.
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MITTELMAN, A.
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MIYAJI, T.
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MIYAMURA, T.
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MIYATA, Y.
6781*, 6800*
MIYAZAKI, K.
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MOCK, D.
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MODAN, M.
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MOHAN, L.C.
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MOHR, U.
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MONACO, A.F. 6956	MLSTAFINA, A.N. 6909*	NIITANI, H. 6935
MONACO, F. 7183*	MUTA, K. 6729*	NIKOLAEV, A.A. 7021
MONIER, R. 6882	MWASI, L.M. 7037	NIKOLOV, P. 7032
MONTAGNIER, L. 6839	MYERS, M.H. 7123	NILES, R.M. 6991*
MONTALEAN, C. 7082*	NAGAO, K. 6768*	NILSSON, K. 6941
MONTIELAR, R.C. 6922*	NAGASE, S. 7188*	NIME, F. 7044*
MONTESANO, R. 6701	NAGATA, C. 6759*	NIME, F.A. 7025
MOODY, E.F.M. 6820*	NAGY, Z. 6674	NISHIMOTO, Y. 6817*
MOFECKI, F. 7106*	NAIMY, N.K. 6724*	NISHIOKA, K. 6931
MOPENO, M. 7105*	NAITO, Y. 6764*	NOCENTINI, S. 6738*
MORERA, F. 7105*	NAKACATE, M. 6759*, 6767*	NOCKE-FINCK, L. 7182*
MORGAN, J.I. 6979*	NAKAMURA, W. 6817*	NOMURA, A. 7119
MORGAN, S.K. 7014	NAKANE, M. 6703	NOMURA, S. 6872, 6876, 7132
MORONI, C. 6891	NAPALIKOV, N.P. 7117	NOMURA, T. 6692
MOROZOVA, K.I. 6811*	NARAYAN, O. 6907*	NOONAN, K.D. 6903*
MORRIS, H.F. 7161	NARISAWA, T. 7043*	NORBERG, B. 7077*
MORROW, W.G. 6808	NARUSE, S. 6766*	NORTJE, C.J. 7062*
MORTON, D.L. 6998*, 6999*, 7006*	NASO, R.B. 6866	NOWELL, P.C. 6972*
MOSCONA, A.A. 6958	NATARAJAN, K.R. 6672	NUSSE, R. 6950
MOSES, R.E. 6820*	NATORI, S. 6736*	OBERLING, F. 7012
MOSS, B. 7157	NAUGHTON, M.A. 6963	O'BRIEN, S.J. 6911*
MOUDEN, A. 6816*	NAVE, E. 6885	ODAKE, G. 6766*
MUCHMORE, A. 7054*	NEELY, M.G. 6762*	ODASHIMA, S. 6767*
MUIR, R.W. 6632	NEEMEH, J.A. 7013	OELSNER, G. 6850
MULLER, C.J.B. 7062*	NEHRING, E.W. 7141*	OESCH, F. 6745*
MULLER, D. 7067*	NELSON, H. 6978*	OESER, H. 6652*
MUNJAL, D. 7072*	NESBIT, M. 7089*	O'EY, J. 7177*
MUNSON, B.F. 6921*	NESMASHNOVA, V.A. 6849	OGIU, T. 6767*
MUNYON, W.H. 6852	NEUBERT, B. 7180*	OHE, K. 6877
MURAD, F. 7165	NEWELL, D.G. 7080*	OHKITA, T. 6763*
MURGITA, R.A. 6923	NICKERSON, P.A. 7178*	OHTA, Y. 6913*
MURPHY, H. 6835	NICKLIN, M.G. 6982*	OKAWA, M. 7097*
MUSIANI, U. 6993*	NIELSEN, L.S. 6930	OKADA, H. 7009
MUSSER, D.A. 6921*	NIEZABITOWSKI, A. 6908*, 7081*	OKAHARA, K. 6789*

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OLDHAM, R. 7054*	PAUL, J. 7155	PLJUSNIN, A.Z. 6836
OLEINICK, N.L. 6823*	PAULSON, D.F. 6864	PLOTNIKOV, I.U.K. 7149*
OLENOV, YU.M. 6608	PAUNIER, L. 7039	PLUZNIN, D.H. 6957
OLIVER, C. 7097*	PAVLOVA, I.V. 6754*	POCOCK, D.H. 6896
OLIVER, J.M. 6638	PAVLOVSKY, A. 7087*	POILEY, S.M. 6889
OLIVIER, L. 6634, 7038	PAVLOVSKY, S. 7010	POLA, V. 6940
OLSSON, L. 7194*	PAWLICKA, E. 6772*	POLLI, E.E. 6639
ONOSAKA, S. 6789*	PAZMINO, L. 6978*	PORTELELLE, D. 6912*
OPELZ, G. 7075*	PEARSE, A. 7050*	PRATT-THOMAS, H.R. 7014
OPPENHEIM, L.B. 6877	PECK, W.A. 6670*	PREHN, L.M. 6662*, 6991*
ORENSTEIN, J.M. 6679	PEEBLES, P.T. 6869	PREHN, R.T. 6662*
OSIPOVA, T.V. 7026	PEILLON, F. 6634, 7038	PREOBRAZHENSKAIA, M.N. 7117
OSTHER, K. 7159	PEN, Y. 7122	PRETTY, H.M. 7013
OTH, D. 6929	PENN, I. 6658*	PREUSSMANN, R. 6719, 6726*
OTHERSEN, H.B. 7014	PERDUE, J.F. 7190*	PREUSSMANN, R.Z. 6753*
OTTO, B. 6860	PEREKREST, V.V. 6895	PRIOR, M.P. 7139*
OUTEIRINO, J. 7082*	PEREZ, C.A. 6666*	PROFFITT, M.R. 6969*
OVERBY, L.R. 6851	PEREZ PINO, M.T. 7082*	PROTSENKO, B.D. 7195*
OWENS, R.B. 7198*	PERIMAN, P.O. 6954	PUMO, D.E. 6880
OZER, H.L. 6955	PERLIN, E. 6954	PURCHASE, H.G. 6831
PALEKAR, A.S. 7018	PERRIS, A.D. 6979*	PURVES, L.R. 7148*
PANET, A. 6842	PERSSON, I. 6930	PYERIN, W.G. 6721
PANI, P.K. 6905*	PETERS, G. 6842	PYLEV, L.N. 6811*
PANIAGUA, G. 7082*	PETO, R. 6708	QUINLAN, D.C. 6901*
PANTELEEV, L.I. 6814*	PETRAKIS, N.L. 6801*	RABES, H.M. 7200*
PAPADOPOULOS, D. 6738*	PETTAVEL, J. 6926	RACADOT, J. 6634, 7038
PARANJPE, M.S. 7174	PETZOLCT, R. 7088*	RACADOT, O. 7038
PARK, W.D. 7197*	PFAFFENBERGER, C.D. 6783*	RACHMELER, M. 6875
PARKS, R.C. 6961	PHILLIPS, M. 7125	RADASKIEWICZ, T. 7091*
PARKS, W.P. 6871	PHILLIPS, R.A. 6628	RALPH, P. 6829
PARMLEY, R.T. 7014	PHILLIPS, S.M. 6962	RAN, M. 6951
PASSOVOY, D. 7001*	PICHUGINA, M.N. 7058*	RANSOM, J.C. 6871
PASTERNAK, C.A. 7176	PICK, A.I. 7060*	RAO, G.A. 7184*

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REICHARD, P.
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REID, B.
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REISFELD, R.A.
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REISSIGL, H.
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RENNER, H.W.
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RENOUX, A.
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RETZEL, E.F.
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REYNOLDS, C.D.
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REZNIK-SCHULLER, H.
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ROBERT-GUROFF, M.
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ROLLER, P.P.
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ROMANO, A.H.
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ROS, E.
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ROSE, N.R.
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RCY, R.M.
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RCYSTON, I.
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RCZMAN, C.
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RUDLAND, P.S.
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RUECKERT, R.R.
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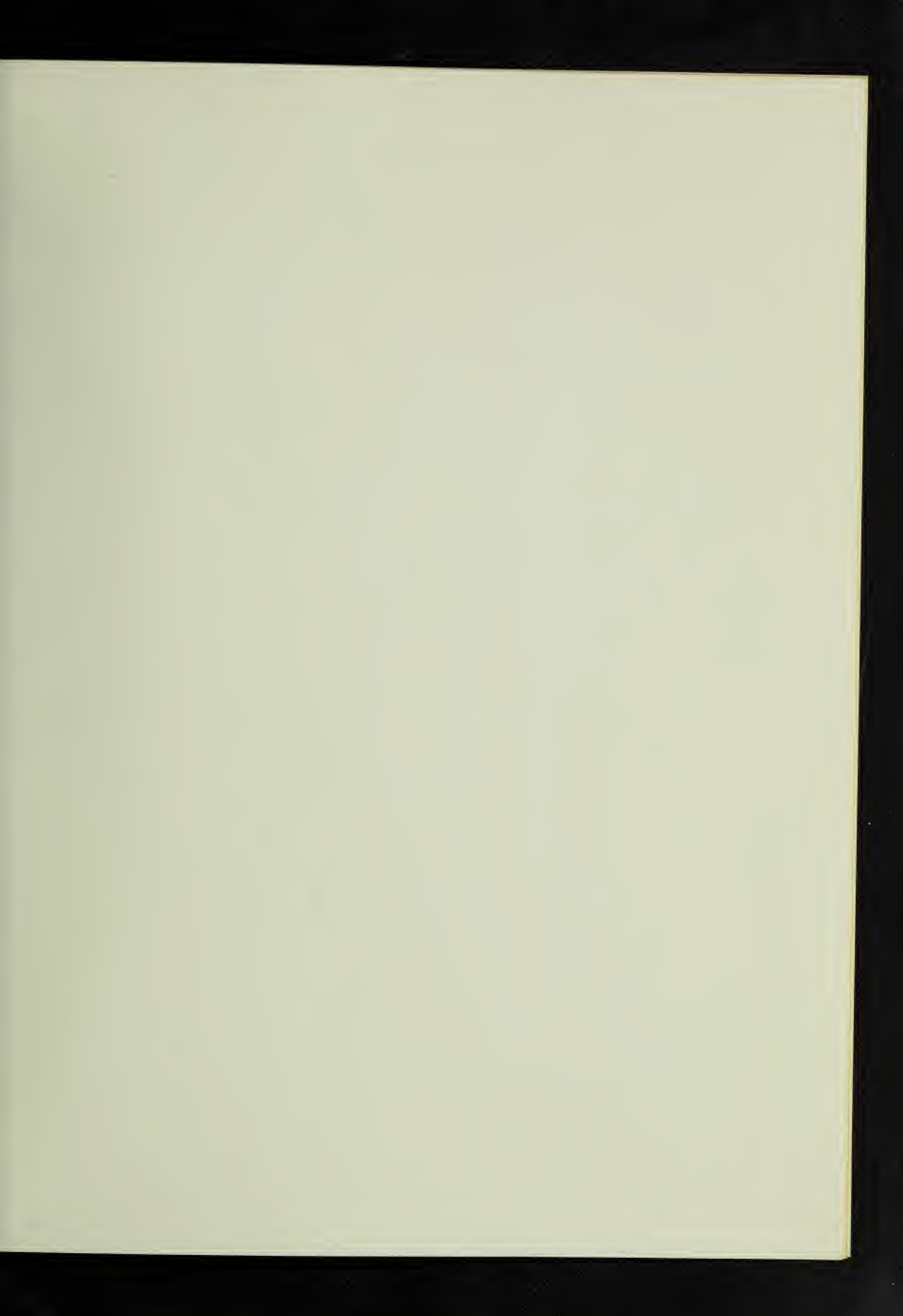
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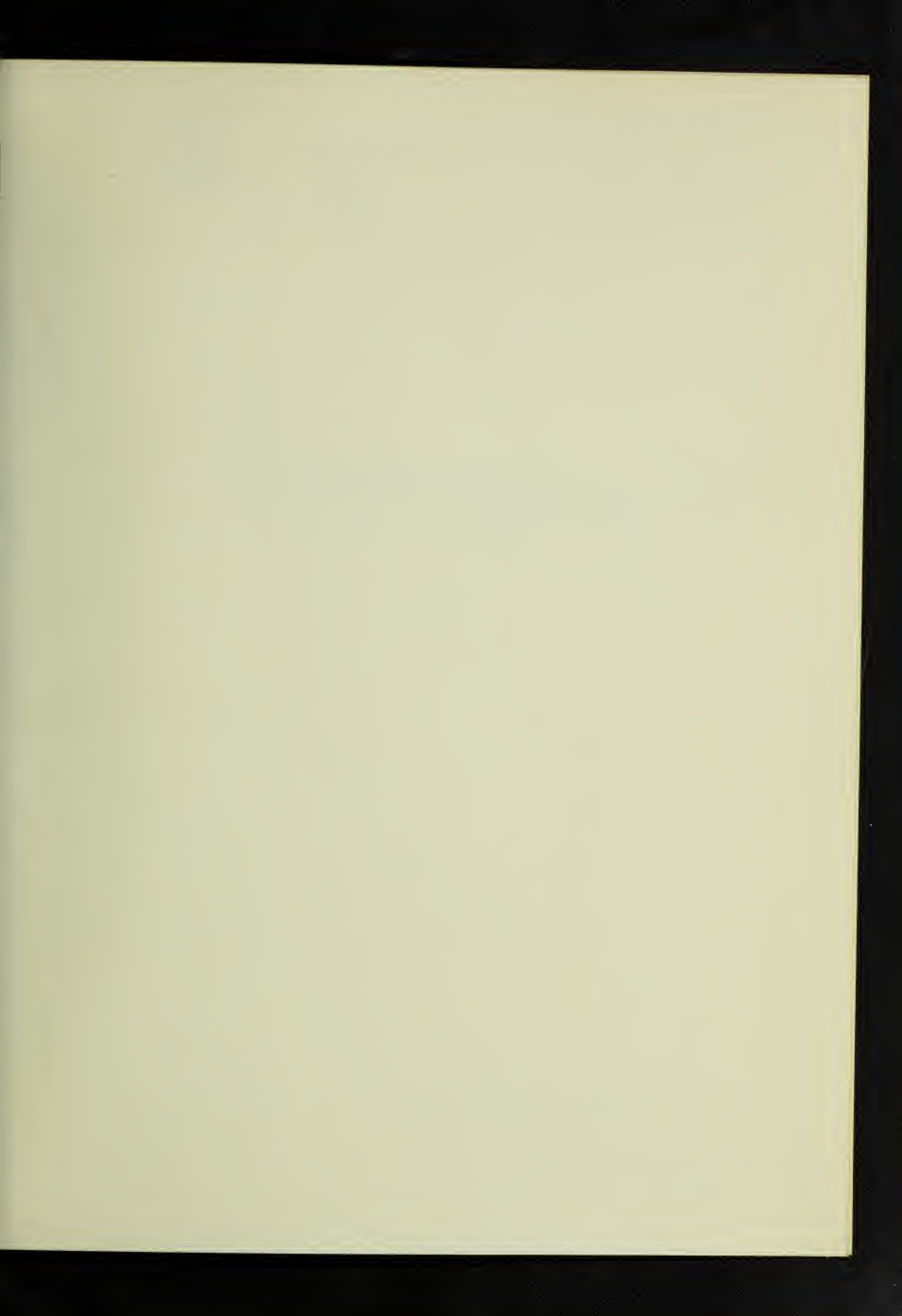
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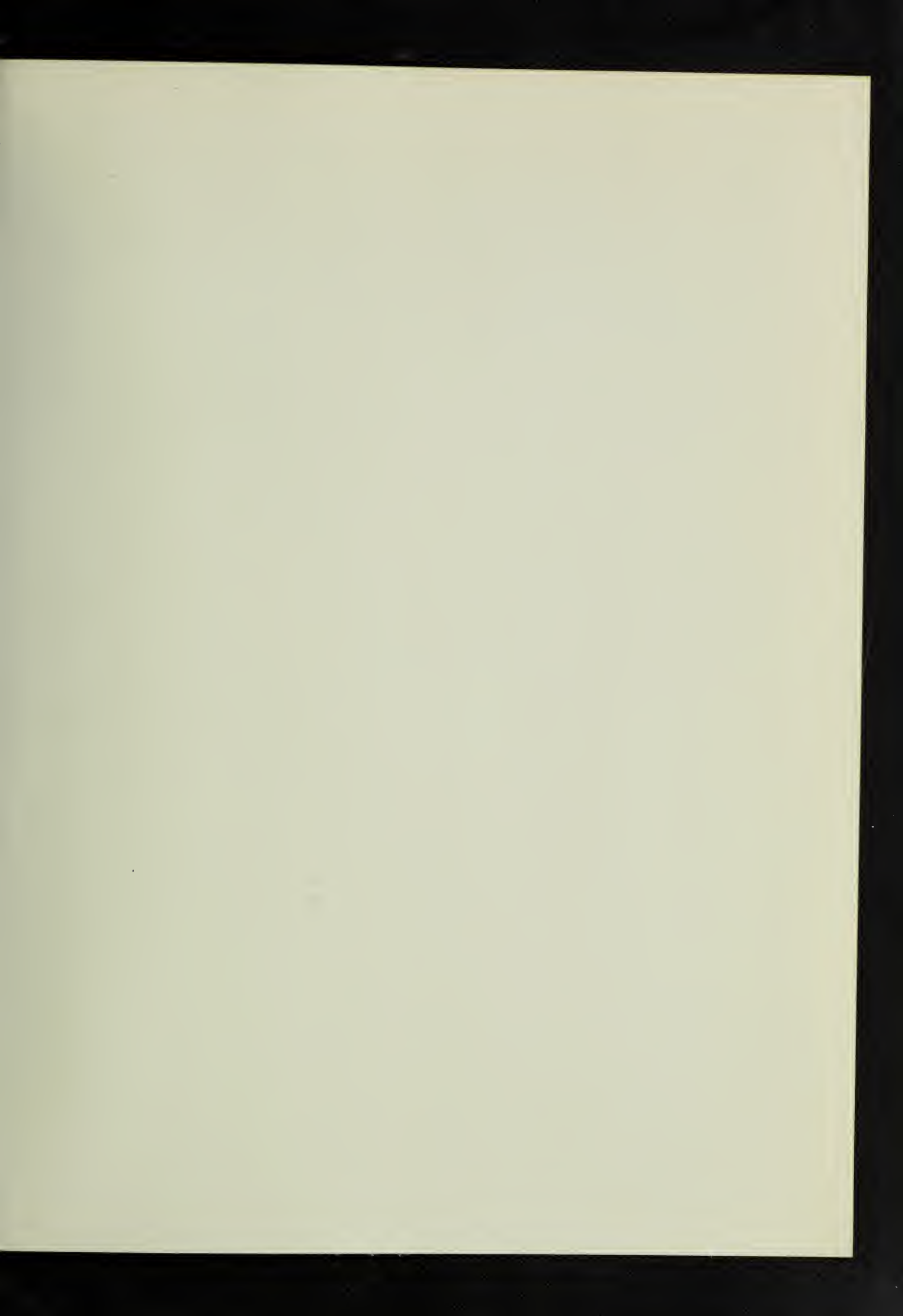
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